Clinical Trial Protocol

A Phase 2 study to assess the safety, efficacy of FLX475 combined with Pembrolizumab in patients with advanced or metastatic gastric cancer

Investigational product	:	FLX475, Pembrolizumab
Protocol number	:	HM-CCRI-201
Version (completion date)	:	3.0 (06-Dec-2022)
Previous version (completion date)	:	2.1 (30-Jun-2021)
Clinical phase	:	Phase 2

※ GENERAL INFORMATION

Protocol No.:	HM-CCRI-201
Date of the Protocol:	06-Dec-2022
Sponsor:	Hanmi Pharmaceutical Co., Ltd. 14, Wiryeseong-daero, Songpa-gu, Seoul, 05545, Korea
Clinical Research Organization:	[redacted]
Sponsor Signatory & Medical Expert:	[redacted]
Coordinating Investigator:	[redacted]

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2 study to assess the safety, efficacy of FLX475 combined with Pembrolizumab in patients with advanced or metastatic gastric cancer

Name of Sponsor: Hanmi Pharmaceutical Co., Ltd.

Name of Investigational Product: FLX475, Pembrolizumab

Principal Investigator: [redacted]

Publication(s): (if applicable)

Planned Study Period:

The end of study is defined as the date when the last subject, last visit (LSLV) occurs or the date at which all required follow-up data and documentation have been received by Sponsor, whichever occurs later. The study is expected to be performed for about 2 years from End of Treatment and the duration may be shorten or extended depending on the study conditions.

Development Phase: 2

Objectives:

To evaluate safety and anti-tumor effect of FLX475 combined with pembrolizumab in subjects with advanced or metastatic gastric cancer. The primary and secondary efficacies will be evaluated by RECIST 1.1 and iRECIST.

Primary Objective:

- To assess the anti-tumor efficacy of FLX475 in combination with pembrolizumab in subjects with advanced or metastatic gastric cancer by RECIST 1.1

Secondary Objectives:

- To assess of the clinical efficacy including Disease Control Rate (DCR), Time to Response (TTR), Duration of Response (DOR) and Progression Free Survival (PFS) by RECIST 1.1
- To assess Overall Survival (OS)
- To assess of the clinical efficacy by iRECIST including iORR, iDCR, iTTR, iDoR, iPFS
- To assess the safety and tolerability of FLX475 combined with pembrolizumab based on Laboratory assessments and Adverse Event (AE), Serious Adverse Events (SAE) using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0

[redacted]

- [redacted]
- [redacted]

Study Design and Treatment Plan:

This clinical study is a Phase 2, open-label study to assess the efficacy, safety profile of FLX475 combined with pembrolizumab in patients with advanced or metastatic gastric cancer. Approximately 90 subjects may be enrolled across two cohorts to examine the safety and efficacy. This study is designed to assess the potential anti-tumor activity when administered at the 100mg QD of FLX475 with pembrolizumab and will be conducted (2) cohorts as detailed below.

- Cohort 1: Checkpoint inhibitor naïve Epstein-Barr Virus (EBV) negative gastric cancer subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer
- Cohort 2: Checkpoint inhibitor naïve EBV positive gastric cancer subjects who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer

Cohort 1 will be enrolled in two-stage, starting with at least 10 subjects in the first stage. Expansion to the stage 2 of cohort 1 will be based on the overall safety and efficacy data as well as any available PK and PD data when the 10th subject completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. During this data review, Sponsor can determine study discontinuation if there is no responder from 10 subjects in the first stage. Once expanded, 20 additional subjects will be accrued in stage 2 and further assessment for the safety and efficacy based on the accumulated data up to 30 subjects (10 from stage 1 and 20 stage 2) will be performed. Referring to the published data[11], 15% of ORR is the minimum criteria to proceed for the next stage in the study. If the posterior probability for the ORR $\geq$ 15% is less than 80%, the enrollment to the cohort will be paused and assessed overall safety along with PK and PD data available. In consideration of the cumulative overall safety and efficacy up to the 30 subjects along with the other competitive landscape, the cohort 1 could be expanded further up to 60 subjects at maximum including the previous subjects enrolled or could be stopped for further enrollment. Also, if required, there could be another stage to investigate further after 2nd stage as well.

Cohort 2 will be enrolled in similar way to the cohort 1 starting with 10 subjects in the first stage and expanded to the second stage based on the overall safety and efficacy as well as available PK and PD data when the 10th subject completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. Referring to the published data[12], for cohort 2 30% of ORR is the minimum criteria to proceed for the next stage in the study. Once determined to the second stage, additional 10 subjects will be enrolled for cohort 2 and If the posterior probability for the ORR ≥ 30% is less than 80%, the enrollment to the cohort will be paused and assess overall safety along with PK and PD data available. If required, further enrollment up to 30 in total as maximum might be performed based on the overall data up to 20 subjects in comparison with the competitive landscape. Also, if required, there could be another stage to investigate further after 2nd stage as well.

The next stage of each cohort will be determined after the comprehensive evaluation from the previous stage by the Independent Data Monitoring Committee(IDMC).

To study potential PD biomarker changes that may be indicative of combined pathway inhibition by the pembrolizumab and FLX475 combination, paired (pre- and post-treatment) tumor biopsies will be obtained from all subjects.

The screening period (Day -30 to Day -1) lasts up to approximately 30 days prior to Cycle 1 Day 1. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. All screened patients will provide written Informed Consent prior to any study procedures.

Once screening procedures are completed and eligibility is confirmed, subjects will start treatment Cycle 1 with FLX475 and pembrolizumab on Day 1. Subject will continue to receive study treatment for an approximate of 2 years (35cycles) or until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification and supportive treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

For subjects who have radiological Progressive Disease (PD) by Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 as determined by the investigator will decide whether the subject can continue to receive study treatment until repeat, confirmatory imaging is obtained using modified RECIST for immunotherapies (iRECIST) for subject management.

Number of Subjects:

As stated in the study design part, each cohort will enroll target subjects separately and both cohorts will initiate 2-stage design. Since the study is to explore safety and efficacy by FLX475 and pembrolizumab, the study size is based on feasibility rather than formal testing. The initial number of target subjects for the 1st stage of both cohorts is determined as 10. However, the target subject number for the 2nd stage would be determined based on the overall safety assessment and the posterior probability of at least 80% to achieve the ORR ≥ 15% and ORR ≥ 30% for cohort 1 and cohort 2, respectively.

The posterior probability for ORR ≥ 15% and ORR ≥ 30% for cohort 1 and 2, respectively, based on the responses in the first and second stage is described in the Table **11.1:1** and Table **11.1:2** assuming uniform prior distribution for ORR as an example.

- Prior distribution for ORR (P) ~ Unif (0,1)
- Observed data X ~ Binomial (N, P)
- Posterior distribution for ORR (P| X) ~ Beta (1+X, 1+N-X)

For example, if we observed 1 response out of the initial 10 subjects of cohort 1 at 1st stage followed by 6 responses out of additional 20 subjects at 2nd stage, we could assume that the probability of ORR ≥ 15% by FLX475 and pembrolizumab combination therapy would be 92% based on the observed data (Table **11.1:1**). Also, if we observed 1 response out of the initial 10 subjects of cohort 2 at 1st stage followed by 7 responses out of additional 10 subjects at 2nd stage, we could assume that the probability of ORR ≥ 30% by FLX475 and pembrolizumab combination therapy would be 85% based on the observed data (Table **11.1:2**). Considering the minimum posterior probability of 80% to achieve the ORR ≥ 15% for cohort 1 and ≥ 30% for cohort 2 as well as the overall safety data, the total number of subjects for each cohort will be adjusted after each stage.

Criteria for Inclusion/ Exclusion:

Patients eligible for enrolment in the study must meet all of the following criteria:

Inclusion Criteria

Patients meeting all of the following criteria must be enrolled in the study:

1. All patients must have histologically or cytologically confirmed, advanced, relapsed or metastatic gastric or gastroesophageal junction adenocarcinoma.
2. Patient is ≥ 18 years of age (or country's legal age of majority if the legal age was > 18 years) at the time of obtaining informed consent.

3. Patient must have one of the following diagnoses to be eligible for enrollment into cohorts:
   A. Cohort 1: Checkpoint inhibitor naïve Epstein-Barr Virus negative (EBV-) gastric cancer patient who has had a disease progression after at least 2 prior systemic treatments for advanced or metastatic gastric cancer
   B. Cohort 2: Checkpoint inhibitor naïve Epstein-Barr virus positive (EBV+) gastric cancer patient (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer
4. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and has a life-expectancy ≥ 3 months.
5. Patient's interval from prior to the first study dose is at least 4 weeks for systemic anticancer therapy including investigational agents (or at least 5 half-lives for investigational/ non-cytotoxic agents, whichever is longer. Upon discussion with the Medical Monitor, fewer than stated wash-out period may be allowed provided that the patient has adequately recovered from any clinically relevant toxicity).
6. Patient must have at least one measurable lesion at baseline by computed tomography(CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Demonstrate adequate organ function as defined in Table **1.1:1**. All screening labs should be performed within 14 calendar days prior to the first study dose.
8. Patient must be willing and able to provide tissue from a newly-obtained biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated). In addition, patient must be willing to provide a tumor biopsy while on treatment at Cycle 2 day 15 (± 3 days) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression. Newly-obtained tissue will be from the stomach and/or gastroesophageal junction or a metastatic location. The post-treatment biopsy specimens should be preferred to collected from the same lesion that was biopsied pre-treatment.

   Note: Newly obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 (Cycle 1) and with no additional anti-cancer treatment having been given after the specimen was obtained. To confirm eligibility, preferred to use archival tissue, but newly obtained biopsy specimens may be replaced for patient unable to submit archival tissue samples. Newly-obtained (FFPE block or tissue in formalin solution) or archived specimens (FFPE block) are preferred to slides.

   Note: The preferred submitting specimen is the FFPE block. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.
9. For female patient of childbearing potential should have a negative serum pregnancy test within 14 calendar days prior to the first study dose.
10. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: a) Not a woman of childbearing potential (WOCBP) b) A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 120 days after the last dose of study treatment.

11. For male patient should agree to use 2 adequate methods of contraception, one of which must be a barrier method, from starting at screening and continue throughout the study period and 120 days after the final dose of study treatment.
12. Ability to swallow tablets without difficulty.
13. Signed and dated written Informed Consent Form by the patient.

Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Has received prior therapy with an anti-PD-1, anti PD-L1, or anti PD-L2 agent or an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137), any history of discontinuing from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).
2. Patient with documented MSI-H status or confirmed by central lab test.
3. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
4. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, (non-infectious) pneumonitis that required steroids, or clinical symptoms of active pneumonitis.
5. Has known active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patient with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
6. Has a known additional malignancy that is progressing or requires active treatment within the past 2 years. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer or any other cancer that has been in complete remission for ≥2 years.
7. Patient has had screening echocardiogram (ECHO) or multiplegated acquisition (MUGA) scan, performed results in a left ventricular ejection fraction (LVEF) that is < 50%.
8. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months prior to start of study treatment, history of cardiac, carotid, or other major cardiovascular surgery, history of valvular heart disease, symptomatic dysrhythmias or unstable dysrhythmias requiring medical therapy, angina requiring therapy, symptomatic peripheral vascular disease, clinically significant history of syncope, New York Heart Association (NYHA) Class 3 or 4

congestive heart failure, or chronic Grade 3 hypertension (diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥160 mmHg).

9. Significant screening electrocardiogram (ECG) abnormalities including atrial fibrillation (unstable or newly diagnosed), double (left and right) bundle branch block, second degree atrioventricular block type II, third-degree atrioventricular block, Grade ≥ 2 bradycardia, QTcF interval ≥ 450 msec, PR interval > 220 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
10. Known family history of sudden cardiac death.
11. Ongoing risk for bleeding due to cancer or bleeding diathesis.
12. Evidence of an ongoing, uncontrolled systemic bacterial, fungal, or viral infection or an uncontrolled local infection requiring therapy at the time of start of study treatment.

    Note: Patient with localized fungal infections of skin or nails are eligible.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection or patient who are HIV seropositive. No HIV testing is required unless mandated by local health authority.
14. Current known active infection of Hepatitis B (defined as HBsAg+ and/or HBeAg+) and high titer of HBV DNA or Hepatitis C virus (defined as Anti-HCV and HCV RNA (+)) infection.
15. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.
16. Has received a live or live-attenuated vaccine within 30 days of planned start of study treatment.

    Note: Administration of killed vaccines are allowed.
17. Has had an allogeneic tissue/solid organ transplant.
18. Males who plan to father children within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment.
19. Major surgery within 28 days (or inadequate recovery from the toxicity or complications of the intervention) before the start of study treatment.

    Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
20. Radiotherapy within 14 days of start of study treatment. Patient must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (i.e., ≤ 14-day course of radiotherapy) to non-CNS lesions.
21. Patient currently receiving treatment with any medications that have the potential to prolong the QT interval and that cannot be either discontinued or substituted with a different medication prior to starting study treatment.
22. Patient currently receiving treatment with strong cytochrome P450 (CYP)3A4 inhibitors or inducers should discontinue such treatment or be switched to a different medication prior to starting study treatment.

23. Current participations in another study of an investigational agent or investigational device within 4 weeks prior to the first dose of study treatment.
24. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results.

Test Product, Dose and Mode of Administration:

[redacted] FLX475 100 mg for oral administration is provided as tablets. All subjects will take FLX475 with water orally once daily (QD) at approximately the same time each day.

Pembrolizumab 200 mg will be administered as an IV infusion over 30 minutes on Day 1 of every 3-week treatment cycle (i.e., every 21 days [±3 days]).

On days when pembrolizumab is also administered (i.e., Day 1 of each cycle), FLX475 should be taken approximately 1 hour before the pembrolizumab infusion.

Duration of Treatment:

Subjects may continue to receive study therapy until the earliest of the following: subject withdrawal from study, confirmed progression of cancer, intolerable study-drug-related toxicity despite appropriate dose modification, the development of intercurrent illness that precludes continued study therapy, pregnancy or breastfeeding, substantial noncompliance with study procedures, completion of Treatment Phase comprising up to 35 treatment cycles for FLX475 and an approximate of 2 years' treatment (35 doses) for pembrolizumab, or study discontinuation.

Criteria for Evaluation:

Efficacy will be assessed according to the RECIST version 1.1 and iRECIST

Safety and tolerability will be assessed using CTCAE version 5.0

Primary Endpoint:

- Objective Response Rate (ORR) by RECIST 1.1

Secondary Endpoints:

- Efficacy in accordance with RECIST 1.1: DCR, TTR, DOR, PFS
- Efficacy in accordance with iRECIST: iORR, iDCR, iTTR, iDOR, iPFS
- Efficacy: OS
- Safety and tolerability: AEs, Laboratory assessments (including hematology, biochemistry, coagulation, urinalysis, vital signs, physical examination, ECG and ECOG)

[redacted]

- [redacted]

Statistical Methods:

Treated Set will include all subjects who received at least one dose of study drug (FLX475 or pembrolizumab). All demographics, Baseline characteristics, efficacy and safety data will be analyzed using the Treated Set as a primary analysis population. Tumor Evaluable Set will include all subject

who are enrolled, complete at least one cycle of investigational drug, and is evaluable for tumor response based on RECIST, version 1.1, and will be used for supportive efficacy analysis.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints unless other specified. As each cohort will enroll target subjects separately and so the analyses will be performed separately by cohort as well. The data summaries will be presented by stage and overall across stages for each cohort.

Efficacy analysis will be conducted based on Treated Set and Tumor Evaluable Set. Tumor-related endpoints will be analyzed based on investigator's assessment using RECIST version 1.1, and the result from assessment using iRECIST also be presented.

The primary efficacy endpoint is Objective Response Rate (ORR) defined as the proportion of subjects whose confirmed best overall response is either Complete Response (CR) or Partial Response (PR) according to RECIST version 1.1. For the efficacy endpoints such as ORR and DCR, frequency and percentage of subjects who have achieved a response will be summarized by stage and 95% 2-sided confidence interval will be calculated by Clopper-Pearson method.

Time-to-event endpoints, including TTR, DoR, PFS and OS, will be summarized descriptively and graphically using Kaplan-Meier (KM) methodology.

According to iRECIST, Best Overall Response (iBOR) of complete response (CR/iCR), partial response (PR/iPR), stable disease (SD/iSD), Progressive disease (iPD) or unevaluable (iUE) will be derived. iORR, iDCR, iTTR, iDoR and iPFS will be analyzed in the same manner as used analyses in accordance with RECIST 1.1.

OS is defined as the duration of time from the treatment start date to time to death from any cause.

The Statistical Analysis Plan (SAP) will include a more technical and detailed description of the statistical analyses.

Extension Part:

The extension part will provide continued access to FLX475 combined with pembrolizumab to subjects who have previously participated in HM-CCRI-201 study and are ongoing from the treatment with clinical benefit.

The primary objective of the extension part mainly is to provide continued treatment with FLX475 combined with pembrolizumab without the previous study procedures that intended to collect data for further analysis (e.g. efficacy, safety, biomarker, etc.).

Detailed information on Extension part are described in Section 17.

Table 1.1:1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematology	
Absolute neutrophil count (ANC)	≥1,500/ μL
Platelets	≥100,000/ μL
Hemoglobin	≥9.0 g/dL or ≥5.6 nmol/L [a]
Renal	
Creatinine OR Measured or calculated [b]creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5X upper limit of normal (ULN) OR ≥30 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤1.5X ULN
AST (SGOT) and ALT (SGPT)	≤2.5X ULN (≤5X ULN for subjects with liver metastases)
Coagulation	
International normalized ratio (INR) OR Prothrombin time (PT) Activated partial thromboplastin time (aPTT) OR partial thromboplastin time (PTT)	≤1.5X ULN unless subject is receiving anticoagulant therapy, as long as PT or aPTT/PTT is within therapeutic range of intended use of anticoagulants

a. Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within the previous 2 weeks.
b. Creatinine clearance (CrCl) should be calculated per institutional standard.

1.2. Schedule of Procedures / Assessments

Table 1.2:1 Schedules of Procedures/Assessments

Study Period/Cycle	Screening	Treatment (Each cycle = 21 days)									End of treatment (EOT) Visit [u]	Follow up	
		Cycle 1			Cycle 2			Cycle 3		Subsequent cycle		Initial Follow up [x]	Long-term Follow up [y]
Cycle day	-30 to -1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)	15 (±3)	1 (±3)	15 (±3)	1 (±3)		30(+7) days after the last dose	Every 3 months after the last dose (±7)
General Procedure													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History [a]	X												
Prior & Concomitant Medication	X[b]	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product Dispensing and Administration													
FLX475 In-clinic Administration [c]		X	X	X	X	X	X	X	X	X			
Pembrolizumab Administration [c]		X			X			X		X			
FLX475 Dispensing [d]		X			X			X		X			
Clinical Procedure/ Assessments [z]													
Physical Examination [e]	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance status	X	X			X			X		X	X		
Vital Signs [f]	X	X	X	X	X	X	X	X	X	X	X		
Triplicate 12-Lead ECGs [g]	X	X	X	X	X	X	X	X		X	X	X	
ECHO or MUGA [h]	X												
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X[v]	X[w]
Diary Card Dispensed/Collected		X			X			X		X	X		

Study Period/Cycle	Screening	Treatment (Each cycle = 21 days)									End of treatment (EOT) Visit [u]	Follow up	
		Cycle 1			Cycle 2			Cycle 3		Subsequent cycle		Initial Follow up [x]	Long-term Follow up [y]
Cycle day	-30 to -1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)	15 (±3)	1 (±3)	15 (±3)	1 (±3)		30(+7) days after the last dose	Every 3 months after the last dose (±7)
Drug Accountability					X			X		X	X		
Laboratory Assessments[aa] and Sample Collection [z]													
Serum Chemistry [i]	X	X	X	X	X	X	X	X	X	X	X		
Hematology [j]	X	X	X	X	X	X	X	X	X	X	X		
Coagulation Tests [k]	X	X			X			X		X	X		
Thyroid Function Tests [l]	X	X						X		X	X		
Urinalysis [m]	X	X			X			X		X	X		
Pregnancy Test [n]	X	X						X		X	X		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]												
[redacted]		[redacted]	[redacted]		[redacted]			[redacted]		[redacted]	[redacted]		
Disease Assessments													
Disease Classification	X												
[redacted]	[redacted]						[redacted]						
Tumor Imaging/Staging (CT/MRI Scan) [s]	X							X		X	X		
Response Assessment [t]								X		X	X		
Survival and Post-Therapy Long-Term Follow-Up													X

All "pre-dose' assessments (including PK and ECGs) should be obtained at study visits even when study treatment is being held or not given.

a. Relevant medical history including current disease and prior treatment, including last prior therapy, best response to last prior therapy (PR, CR, SD, or PD) and either time on last therapy or duration of response.
b. Includes medications taken within 30 days prior to screening.
c. On days when a clinical visit, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle. After a new supply of drug has been dispensed for that cycle, a diary card will be provided to each subject for recording of all dose administration information for drug accountability purposes. Pembrolizumab will be administered at a dose of 200mg IV over 30 minutes on Day 1 of each cycle. Pembrolizumab infusion should occur at at least 1 hour after the dose of FLX475 is administered in the clinic. (Treatment cycles will be counted continuously regardless of dose interruptions and assessments corresponding to each cycle should be performed regardless of study drug administration).
d. Dispensing of 3-week supply of FLX475 to the subject with instruction for self-administration at home.
e. Height measurement performed only at screening. Weight measurement should be performed at screening and on Day 1 of each cycle and at ED/EOT.
f. Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected with the subject in a sitting position. [redacted]
g. Triplicate ECGs with tracings approximately 2 minutes apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. ECGs assessment will precede blood sampling if they are to be overlapped. [redacted]
h. ECHO or MUGA scans are to be performed at Screening unless the recent result within 30 days prior to Day 1 of Cycle 1 is available. Additional assessment may be performed if clinically required at investigator's discretion.
i. Serum Chemistry: including sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine (or CrCl), uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Serum Chemistry to be obtained pre-dose at

screening visit, study visit days and at ED/EOT. Laboratory Screening Tests should be performed within 14 calendar days prior to the first study dose.

j. Hematology: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. Blood sampling for hematology to be obtained pre-dose at screening visit, study visit days and at ED/EOT. Laboratory Screening Tests should be performed within 14 days prior to the first study dose.

k. Coagulation Tests (PT, PTT or aPTT, and INR) should be obtained pre-dose at screening visit, day 1 of every cycle and at ED/EOT. Laboratory Screening Tests should be performed within 14 calendar days prior to the first study dose.

l. Thyroid function tests should be obtained at screening, pre-dose on Day 1 of Cycle 1 and every odd-numbered cycle during study treatment (e.g., Cycle 3, 5, etc.) and at ED/EOT. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).

m. Urinalysis will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).

n. Pregnancy test only in women of childbearing potential during screening by serum test. Urine or serum pregnancy test at all other time points. After Cycle 1, pregnancy testing will be performed on Day 1 of every odd-numbered cycle (e.g., Cycle 3, 5, etc.) and at ED/EOT.

[redacted]

s. Tumor Imaging/Staging (CT/MRI Scan): After baseline scan, response assessments will be performed on screening, C3D1 (±7 days) and on Day 1 (±7 days) of every 6 weeks for the first year, followed by Day1 (±7 days) of every 3 Cycles thereafter for up to 2 years and at any time per investigator's discretion. Confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective

response. If previous imaging was performed within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

t. Response Assessment: Initial response assessment will be performed after the first 2 cycles, then every 2 cycles for the first year, followed by every 3 cycles thereafter for up to 2 years (i.e., ±7 days of C3D1, C5D1, etc.) and at any time per investigator's discretion and at ED/EOT (unless clear PD has been documented previously).

u. All Early Discontinuation / End of Study Treatment (ED/EOT) assessments must be performed within 14 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first.

v. All AEs must be recorded and followed through 30 days following cessation of study treatment (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first.

w. Serious adverse events will be collected after the consent form is signed through 90 days following cessation of study treatment, or 30 days after final dose if the subject initiates new anticancer therapy, whichever occurs first.

x. 30 days from the final dose of study treatment.

y. Data regarding post-study anti-tumor therapy and survival will be collected from all subjects who receive ≥ 1 dose of FLX475 or pembrolizumab. All subjects who discontinue study drug will be followed for survival and any post-study anticancer treatment via at least every 3 months (±7 days). This long-term follow-up information will be gathered during routine clinic visits, other site contact with the subjects, or via telephone or e-mail with the subjects/caregivers or referring physician offices. These data will be collected in the source documents (e.g., subject medical record) and transcribed into a specific eCRF.

z. All time points of the assessments are based on FLX475 administration.

aa. Laboratory Screening Tests (Serum chemistry, hematology, coagulation tests, thyroid function) should be performed within 14 calendar days prior to the first study dose.

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3. INTRODUCTION

3.1. Background

3.1.1. Immunotherapy for Cancer

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells (T_{eff}) to FoxP3+ regulatory T-cells (T_{reg}) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [2,3].

The programmed cell death-1 receptor-ligand (PD-1/PD-L1) interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [4,5].

The recent use of antibodies (known as checkpoint inhibitors, or CPIs) to block immune checkpoints such as PD-1 and CTLA-4 has resulted in meaningful anti-tumor immune responses in multiple types of cancer [6,7,8]. However, only a minor subset of patients experiences deep and durable responses to these treatments. Because activated immune responses are naturally controlled from running unchecked and causing autoimmunity not only by these suppressive checkpoint signals, but also by immunosuppressive cells such as T_{reg} and suppressive myeloid cells, more effective anti-tumor immunotherapy treatments may also need to address the accumulation of T_{reg} in and around tumors which can inhibit cytotoxic (effector) T-cells (T_{eff}) from killing tumor cells [9].

T_{reg} are recruited into tumors by small secreted protein signals called chemokines – specifically C-C motif chemokine ligand 17 (CCL17, or Thymus and activation-regulated chemokine) and C-C motif chemokine ligand 22 (CCL22, macrophage-derived chemokine) – produced by tumor cells and other cells in the tumor microenvironment (TME). These chemokines serve as a “homing signal” to T_{reg} by binding to their cognate receptor, C C chemokine receptor type 4 (CCR4), which is expressed on nearly all human T_{reg} [10]. [redacted]

3.1.2. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and has been approved as an intravenous (IV) immunotherapy for several advanced malignancies. Keytruda® (Pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to the approved labeling and Investigator’s Brochure for more details on specific indications and for detailed background information on Keytruda® (Pembrolizumab, MK-3475) (Keytruda Investigator’s Brochure).

The structure of murine PD-1 has been resolved [22]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [5,17,19,21]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [18,20]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced or metastatic gastric cancer.

3.1.3. FLX475

FLX475, also known as [redacted], is an orally available, potent and selective small-molecule antagonist of CCR4. In preclinical models of cancer, it has been shown to inhibit the recruitment of T_{reg} into tumors, and to improve tumor control and eradication in combination with CPIs.

In a Phase 1 clinical trial in 104 healthy volunteers (FLX475-01), FLX475 was well tolerated and demonstrated favorable pharmacokinetic properties and target engagement [13]. FLX475 is currently being studied in an ongoing Phase 1/2 study trial of FLX475 (FLX475-02, NCT03674567) in patients with advanced cancer which is examining the safety, pharmacokinetics, pharmacodynamics (PD), and anti-tumor activity of daily dosing both of FLX475 monotherapy, and in combination with a CPI (pembrolizumab). This trial, sponsored by RAPT Therapeutics, is currently underway in approximately 30 clinical sites in the United States, Australia, South Korea, Taiwan, Thailand, and Hong Kong [14].

3.1.3.1. Pre-clinical Experience with FLX475

3.1.3.1.1. Non-Clinical Pharmacology

[redacted]

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [23-29]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [22,23,27,29,30]. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition

involved local infiltration and activation of effector T cell function in vivo [23]. Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models. For more details on non-clinical studies, refer to the FLX475 Investigator's Brochure.

[redacted]

3.1.3.1.2. Preclinical Pharmacokinetics

FLX475 has been given orally and intravenously to mice, rats, dogs, and monkeys and was absorbed and bioavailable in all species tested. Following single and repeated doses in mice and dogs, exposure is similar in males and females. Exposure (C_{max} and AUC_{0-24}), increases with the increase in dose level in both species and there is a small degree of accumulation (~2 fold) with repeated dosing.

CYP3A4 is likely responsible for the metabolism of FLX475. Metabolites present in human hepatocyte incubations were also detected in the incubation of at least one of the species used for toxicity assessment (mouse or dog).

[redacted]

3.1.3.1.3. Preclinical Toxicology

The non-clinical toxicology program in support of FLX475 included both in vivo and in vitro evaluations, consisting of a core battery of safety pharmacology, genotoxicity, and repeat dose toxicity studies with a treatment duration of up to 4 weeks. The in vivo studies were conducted in mice and dogs administered FLX475 via daily oral dosing, the intended frequency and route of administration in humans. [redacted] Reversible gastrointestinal effects (epithelial degeneration/necrosis noted primarily in the stomach) were the key FLX475 related effects in the 4-week oral toxicity studies in mice and dogs. These effects were associated with body weight loss and decreased food consumption, emesis, vomitus, and/or excessive salivation. Lymphoid depletion in the lymphoid tissues was consistent with an inflammatory/stress response, likely secondary and attributable to stress associated with degeneration/necrosis in the stomach.

In the 4-week dog study, the no-observed-adverse-effect level (NOAEL) was 5 mg/kg/day and highest non-severely toxic dose (HNSTD) was 15 mg/kg/day. In the 4-week mouse study, the NOAEL was 10 mg/kg/day and severely toxic dose was at least 60 mg/kg/day. The results from these studies support a proposed starting dose of 25 mg (QD) FLX475 in oncology patients.

3.1.3.2. Clinical Experience with FLX475

3.1.3.2.1. Phase 1 Healthy Volunteer Study

FLX475 has been studied in a Phase 1, first-in-human, randomized, double-blind, placebo-controlled trial in the Netherlands examining the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of both

single and repeat dosing of FLX475 in healthy volunteers [**13**]. Seven cohorts of 8 subjects each (6 drug, 2 placebo) were administered single doses ranging from 5 mg to 1000 mg. Six cohorts were administered daily doses of FLX475 for 14 days ranging from 25 mg to 150 mg, including two cohorts evaluating a 300 mg loading dose administered on Day 1.

FLX475 was well-tolerated, with no significant laboratory abnormalities or dose-limiting clinical adverse events. Dose-dependent increases in exposure were observed with low peak to-trough ratios and a half-life of approximately 72 hours. Daily dosing without a loading dose demonstrated approximately 4–5x accumulation of FLX475 over 14 days. The tablet formulation of FLX475 to be used in the oncology study was shown to provide equivalent exposure as the capsule formulation used in the healthy volunteer (HV) study, suggesting the HV PK data are applicable to the planned study in cancer patients. In addition, there was no significant effect of food on the bioavailability or PK profile of FLX475 tablets. A receptor occupancy (RO) PD assay using study subject peripheral blood T_{reg} demonstrated a tight PK/PD relationship, suggesting that doses of approximately 75 mg PO QD and above are sufficient to maintain target drug exposure above the IC_{90} for human in vitro T_{reg} migration.

The most common adverse events reported were transient low-grade headache and gastrointestinal symptoms (e.g. loose stool, abdominal discomfort, vomiting) that were considered not, unlikely, or possibly related to study medication. Asymptomatic transient Grade 1 and 2 prolongations in QTcF interval were occasionally observed during dose escalation. An increased number of QTcF interval increases were observed at the highest dose cohorts which achieved mean Cmax values approximately 3–5-fold greater than the target therapeutic exposure level. There was no notable increase in QTcF interval prolongation events observed at dose levels and exposures within the target exposure range for clinical efficacy.

3.1.3.2.2. **Phase 1/2 Advanced Cancer Study**

In the ongoing FLX475-02 Phase 1/2 study in patients with advanced cancer, Phase 1 dose escalation has been completed for both FLX475 monotherapy and FLX475 + pembrolizumab combination therapy, and a recommended Phase 2 dose of 100 mg QD for FLX475 has been selected, based on the cumulative PK, PD, and safety data for both FLX475 monotherapy and combination therapy.

In Part 1a of the FLX475-02 study (Phase 1 dose escalation of FLX475 monotherapy), 19 subjects with advanced cancer (including gastric and gastroesophageal cancer) have been treated in four dose escalation cohorts with daily dosing of FLX475 at 25 mg (3 subjects), 50 mg (3 subjects), 75 mg (7 subjects), and 100 mg (6 subjects). PK, PD, and safety findings have been consistent with what was observed in the healthy volunteer study. While one dose-limiting clinical adverse event of asymptomatic QTc prolongation (> 500 ms and > 60 ms prolongation from baseline) was observed in each of the 75 mg and 100 mg monotherapy dose escalation cohorts, both in subjects with confounding factors (including an elevated and increasing QTc at baseline in one, and hypokalemia in the other), no monotherapy maximum tolerated dose (MTD) was defined as no dose was determined to have exceeded the MTD. Preliminary PK data demonstrated that all 6 subjects in the 100 mg cohort achieved or exceeded the target minimum FLX475 drug exposure level of 130 ng/mL after 1 week of dosing. Available PD (RO) data suggested all subjects achieved target RO levels of 75% or more. Based on the results of the healthy volunteer study, it was expected that additional dose escalation beyond 100 mg (e.g. 125 mg and beyond) was unnecessary to improve target drug exposure and RO, and would likely eventually exceed an MTD due to QTcF prolongation observed. Therefore 100 mg was chosen as the recommended Phase 2 dose (RP2D) for FLX475 FLX 475 monotherapy.

In Part 1b of the FLX475-02 study (Phase 1 dose escalation of FLX475 + pembrolizumab combination therapy), 18 subjects with advanced cancer have been treated in three dose escalation cohorts with standard-dose pembrolizumab plus daily dosing of FLX475 at 50 mg (3 subjects), 75 mg (4 subjects), and 100 mg (11 subjects). PK, PD, and safety findings have been consistent with what was observed in the healthy volunteer study (FLX475-01) and in Part 1a of FLX475-02. PK of FLX475 was similar between monotherapy and combination therapy cohorts. Preliminary PK data demonstrated that all evaluable subjects in the 100 mg combination cohort achieved or exceeded the target minimum FLX475 drug exposure level of 130 ng/mL after 1 week of dosing. Available PD (RO) data suggested all evaluable

subjects in the 100 mg combination cohort achieved target RO levels of 75% or more. No new or unexpected treatment-emergent adverse events (TEAEs) were observed with the combination of FLX475 + pembrolizumab, i.e. all TEAEs observed were similar to those previously observed with either FLX475 monotherapy or pembrolizumab monotherapy alone. Finally, no DLTs were observed in all DLT-evaluable subjects at the highest combination dose of 100 mg FLX475. Therefore 100 mg FLX475 PO QD + 200 mg pembrolizumab IV Q3 weeks was selected as the RP2D for combination therapy, as additional dose escalation would be unnecessary to improve target drug exposure and RO, and would likely eventually exceed an MTD due to predicted QTcF prolongation at higher exposures.

3.2. Benefit/Risk Assessment

[redacted] The primary dose-related effects observed in non-clinical toxicology studies included gastrointestinal-related effects (e.g. emesis, decreased food consumption, weight loss) and borderline QTcF prolongation. However, these findings occurred at dose levels several-fold higher than the predicted therapeutic dose range and would also be expected to be easily monitorable and reversible in the clinic. In the clinical experience in healthy volunteers and in patients with advanced cancer to date [Section **3.1.3.2**], only asymptomatic and reversible QTcF prolongation has been observed as a dose-related effect of FLX475, and a daily oral dose of 100 mg FLX475 has been chosen as the recommended Phase 2 dose of FLX475 to be used in patients with advanced cancer, both as monotherapy, and in combination with pembrolizumab.

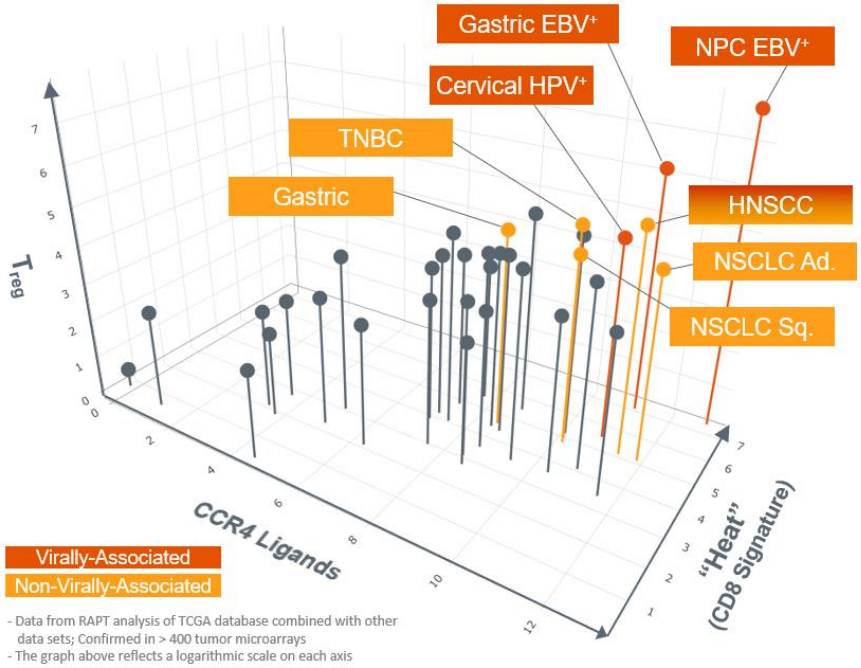
Thus, based on the available preclinical, non-clinical, and clinical data, the risk-benefit profile of FLX475 is judged acceptable for this proposed Phase 2 study in subjects with advanced cancer. No significant safety findings have been observed [Section **3.1.3.2**] that would alter the risk-benefit profile of this proposed phase 2 study testing FLX475 combination therapy with pembrolizumab in subjects with advanced or metastatic gastric cancer.

[redacted] The safety profile of pembrolizumab has been well described, and does include immune-mediated toxicity (Keytruda Investigator's Brochure). Based on its proposed mechanism of action, FLX475 is not expected to significantly enhance immune mediated toxicity when administered with pembrolizumab. However, signs and symptoms of immune-mediated toxicity (e.g., autoimmunity) will be closely monitored in the clinic and appropriate supportive care measures will be administered as indicated.

3.3. Study Rationale

Based upon the proposed mechanism of action of FLX475, it is predicted that [redacted], should have the greatest chance of benefitting from FLX475 treatment, as they should have the necessary components to generate a potent anti-tumor immune response, but are limited by the presence of T_{reg}. Analysis of data from The Cancer Genome Atlas database and additional published sources has identified certain tumor types enriched for all of these gene signatures, referred to as "charged" tumors [**15**] (Figure **3.3:1**).

Figure 3.3:1 Identification and Characterization of "Charged" Tumors



The ongoing Phase 1/2 trial of FLX475 (FLX475-02, NCT03674567) in patients with advanced cancer is examining the safety, pharmacokinetics, pharmacodynamics (PD), and anti-tumor activity of daily dosing both FLX475 monotherapy, and in combination with a CPI (pembrolizumab). This trial, sponsored by RAPT Therapeutics, is currently underway in approximately 30 clinical sites in the United States, Australia, South Korea, Taiwan, Thailand, and Hong Kong, and is specifically focused on enrolling the following "charged" tumor types in Phase 2: nasopharyngeal cancer (NPC), EBV+ lymphoma, head and neck squamous cell carcinoma (HNSCC), cervical cancer, non-small cell lung cancer (NSCLC), and triple-negative breast cancer (TNBC) [14].

This Phase 2 study will evaluate efficacy, safety, PK, pharmacodynamics (PD), in addition to potential changes in the TME and possible clinical efficacy of FLX475 in combination with pembrolizumab in subjects with two additional subtypes of "charged" tumors not currently included in the Phase 2 portion of the FLX475-02 study: advanced or metastatic gastric cancer and EBV+ gastric cancer.

The primary hypothesis of this study is that FLX475 in combination with pembrolizumab will achieve an efficacy, acceptable safety, tolerability, and PK profile in subjects with advanced or metastatic gastric cancer. [redacted]

4. OBJECTIVES

To evaluate safety and anti-tumoral effect of FLX475 combined with pembrolizumab in subjects with advanced or metastatic gastric cancer. The primary and secondary efficacies will be evaluated by RECIST 1.1 and iRECIST.

4.1. Primary Objectives

- To assess the anti-tumor efficacy of FLX475 in combination with pembrolizumab in subjects with advanced or metastatic gastric cancer by Objective Response Rate (ORR) by RECIST 1.1

4.2. Secondary Objectives

- To assess of the clinical efficacy including DCR (complete response + partial response + stable response), TTR, DoR, and PFS by RECIST 1.1
- To assess OS
- To assess of the clinical efficacy by iRECIST including iORR, iDCR, iTTR, iDoR, iPFS
- To assess the safety and tolerability of FLX475 combined with pembrolizumab based on Laboratory assessments and AE, SAE using NCI-CTCAE v 5.0

5. STUDY DESIGN

5.1. Overall Design and Plan

This clinical study is a Phase 2, open-label study to assess the efficacy, safety profile of FLX475 combined with pembrolizumab in patients with advanced or metastatic gastric cancer. Approximately 90 subjects may be enrolled across two cohorts to examine the safety and efficacy. This study is designed to assess the potential anti-tumor activity when administered at the 100mg QD of FLX475 with pembrolizumab and will be conducted (2) cohorts as detailed below.

Cohort 1: Checkpoint inhibitor naïve Epstein-Barr Virus (EBV) negative gastric cancer subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer

Cohort 2: Checkpoint inhibitor naïve Epstein-Barr Virus (EBV) positive gastric cancer subjects who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer

Cohort 1 will be enrolled in two stages, starting with at least 10 subjects in the first stage. Expansion to the stage 2 of cohort 1 will be based on the overall safety and efficacy data as well as any available PK and PD data when the 10^{th} subject completes 4 cycles (or 12 weeks; after 2^{nd} response assessment) or withdrawn from the study, whichever occurs first. During this data review, Sponsor can determine study discontinuation if there is no responder from 10 subjects in the first stage. Once expanded, 20 additional subjects will be accrued in stage 2 and further assessment for the safety and efficacy based on the accumulated data up to 30 subjects (10 from stage 1 and 20 stage 2) will be performed. Referring to the published data[11], 15% of ORR is the minimum criteria to proceed for the next stage in the study. If the posterior probability for the ORR $\geq$ 15% is less than 80%, the enrollment to the cohort will be paused and assessed overall safety along with PK and PD data available. In consideration of the cumulative overall safety and efficacy up to the 30 subjects along with the other competitive landscape, the cohort 1 could be expanded further up to 60 subjects at maximum including the previous subjects enrolled or could be stopped for further enrollment. Also, if required, there could be another stage to investigate further after 2nd stage as well.

Cohort 2 will be enrolled in similar way to the cohort 1 starting with 10 subjects in the first stage and expanded to the second stage based on the overall safety and efficacy as well as available PK and PD data when the 10^{th} subject completes 4 cycles (or 12 weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. During this data review, Sponsor can determine study discontinuation if there is no responder from 10 subjects in the first stage same as cohort 1. Referring to the published data[12], for cohort 2 30% of ORR is the minimum criteria to proceed for the next stage in the study. Once determined to the second stage, additional 10 subjects will be enrolled for cohort 2 and If the posterior probability for the ORR ≥ 30% is less than 80%, the enrollment to the cohort will be paused and assess overall safety along with PK and PD data available. If required, further enrollment up to 30 in total as maximum might be performed based on the overall data up to 20 subjects in comparison with the competitive landscape. Also, if required, there could be another stage to investigate further after 2nd stage as well.

The next stage of each cohort will be determined after the comprehensive evaluation from the previous stage by the Independent Data Monitoring Committee(IDMC).

To study potential PD biomarker changes that may be indicative of combined pathway inhibition by the pembrolizumab and FLX475 combination, paired (pre- and post-treatment) tumor biopsies will be obtained from all subjects.

The screening period (Day -30 to Day -1) lasts up to approximately 30 days prior to Cycle 1 Day 1. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. All screened patients will provide written Informed Consent prior to any study procedures.

Once screening procedures are completed and eligibility is confirmed, subjects will start treatment Cycle 1 with FLX475 and pembrolizumab on Day 1. Subject will continue to receive study treatment for a maximum of 35 cycles (approximately 2 years) or until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification and supportive treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

For subjects who have radiological Progressive Disease (PD) by Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 as determined by the investigator will decide whether the subject can continue to receive study treatment until repeat, confirmatory imaging is obtained using modified RECIST for immunotherapies (iRECIST) for subject management.

5.2. End of Study and Length of Study

The end of study is defined as the date when the last subject, last visit (LSLV) occurs or the date at which all required follow-up data and documentation have been received by Sponsor, whichever occurs later. The study is expected to be performed for about 2 years from End of Treatment visit of last subject and the duration may be shorten or extended depending on the study conditions.

6. STUDY POPULATION

6.1. Inclusion Criteria

Patients meeting all of the following criteria must be enrolled in the study:

1. All patients must have histologically or cytologically confirmed, advanced, relapsed or metastatic gastric or gastroesophageal junction adenocarcinoma.
2. Patient is ≥ 18 years of age (or country's legal age of majority if the legal age was > 18 years) at the time of obtaining informed consent.
3. Patient must have one of the following diagnoses to be eligible for enrollment into cohorts:
   A. Cohort 1: Checkpoint inhibitor naïve Epstein-Barr Virus negative (EBV-) gastric cancer patient who has had a disease progression after at least 2 prior systemic treatments for advanced or metastatic gastric cancer
   B. Cohort 2: Checkpoint inhibitor naïve Epstein-Barr virus positive (EBV+) gastric cancer patient (as determined by standard methods, e.g. EBER ISH or LMP-1 IHC) who had at least 1 prior systemic treatment for advanced or metastatic gastric cancer
4. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and has a life-expectancy ≥ 3 months.
5. Patient's interval from prior to the first study dose is at least 4 weeks for systemic anticancer therapy including investigational agents (or at least 5 half-lives for investigational/ non-cytotoxic agents, whichever is longer. Upon discussion with the Medical Monitor, fewer than stated wash-out period may be allowed provided that the patient has adequately recovered from any clinically relevant toxicity).
6. Patient must have at least one measurable lesion at baseline by computed tomography(CT) or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Demonstrate adequate organ function as defined in Table **1.1:1**. All screening labs should be performed within 14 calendar days prior to the first study dose.
8. Patient must be willing and able to provide tissue from a newly-obtained biopsy of a tumor lesion not previously irradiated (unless subsequent progression demonstrated). In addition, patient must be willing to provide a tumor biopsy while on treatment at Cycle 2 day 15 (±3 days) and may be asked to provide additional biopsies at other timepoints such as the time of discontinuation due to progression. Newly-obtained tissue will be from the stomach and/or gastroesophageal junction or a metastatic location. The post-treatment biopsy specimens should be preferred to collected from the same lesion that was biopsied pre-treatment.

   Note: Newly obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 (Cycle 1) and with no additional anti-cancer treatment having been given after the specimen was obtained. To confirm eligibility, preferred to use archival tissue, but newly obtained biopsy specimens may be replaced for patient unable to submit

archival tissue samples. Newly-obtained (FFPE block or tissue in formalin solution) or archived specimens (FFPE block) are preferred to slides.

Note: The preferred submitting specimen is the FFPE block. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory Details pertaining to tumor tissue submission can be found in the Laboratory Manual.

9. For female patient of childbearing potential should have a negative serum pregnancy test within 14 calendar days prior to the first study dose.
10. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: a) Not a woman of childbearing potential (WOCBP) b) A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 120 days after the last dose of study treatment.
11. For male patient should agree to use 2 adequate methods of contraception, one of which must be a barrier method, from starting at screening and continue throughout the study period and 120 days after the final dose of study treatment.
12. Ability to swallow tablets without difficulty.
13. Signed and dated written Informed Consent Form by the patient.

6.2. Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137), any history of discontinuing from that treatment due to Grade 3 or higher immune-related adverse event (irAE).
2. Patient with documented MSI-H status or confirmed by central lab test.
3. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
4. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, (non-infectious) pneumonitis that required steroids, or clinical symptoms of active pneumonitis.
5. Has known active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patient with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer or any other cancer that has been in complete remission for ≥2 years.

7. Patient has had screening echocardiogram (ECHO) or multiplegated acquisition (MUGA) scan performed results in a left ventricular ejection fraction (LVEF) that is < 50%.
8. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months prior to start of study treatment, history of cardiac, carotid, or other major cardiovascular surgery, history of valvular heart disease, symptomatic dysrhythmias or unstable dysrhythmias requiring medical therapy, angina requiring therapy, symptomatic peripheral vascular disease, clinically significant history of syncope, New York Heart Association (NYHA) Class 3 or 4 congestive heart failure, or chronic Grade 3 hypertension (diastolic blood pressure ≥ 100 mmHg or systolic blood pressure ≥160 mmHg).
9. Significant screening electrocardiogram (ECG) abnormalities including atrial fibrillation (unstable or newly diagnosed), double (left and right) bundle branch block, second degree atrioventricular block type II, third-degree atrioventricular block, Grade ≥ 2 bradycardia, QTcF interval ≥ 450 msec, PR interval > 220 msec, or unstable cardiac arrhythmia requiring medication. Chronic asymptomatic atrial fibrillation stably controlled with medications is permitted.
10. Known family history of sudden cardiac death.
11. Ongoing risk for bleeding due to cancer or bleeding diathesis.
12. Evidence of an ongoing, uncontrolled systemic bacterial, fungal, or viral infection or an uncontrolled local infection requiring therapy at the time of start of study treatment.

    Note: Patient with localized fungal infections of skin or nails are eligible.
13. Has a known history of Human Immunodeficiency Virus (HIV) infection or patient who are HIV seropositive. No HIV testing is required unless mandated by local health authority.
14. Current known active infection of Hepatitis B (defined as HBsAg+ and/or HBeAg+) and high titer of HBV DNA or Hepatitis C virus (defined as Anti-HCV and HCV RNA (+)) infection.
15. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.
16. Has received a live or live-attenuated vaccine within 30 days of planned start of study treatment.

    Note: Administration of killed vaccines are allowed.
17. Has had an allogeneic tissue/solid organ transplant.
18. Males who plan to father children within the projected duration of the study, starting with the screening visit through 120 days after the final dose of study treatment.
19. Major surgery within 28 days (or inadequate recovery from the toxicity or complications of the intervention) before the start of study treatment.

    Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
20. Radiotherapy within 14 days of start of study treatment. Patient must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (i.e., ≤ 14-day course of radiotherapy) to non-CNS lesions.
21. Patient currently receiving treatment with any medications that have the potential to prolong the QT interval and that cannot be either discontinued or substituted with a different medication prior to starting study treatment.

22. Patient currently receiving treatment with strong cytochrome P450 (CYP)3A4 inhibitors or inducers should discontinue such treatment or be switched to a different medication prior to starting study treatment.
23. Current participations in another study of an investigational agent or investigational device within 4 weeks prior to the first dose of study.
24. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results.

7. TREATMENT

7.1. Dose Rationale for Combination Therapy

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.2. Pembrolizumab

The planned dose of Pembrolizumab (Keytruda®) for this study is 200 mg every 3 weeks (Q3W), which is the currently approved dosage for treatment of advanced cancer. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all cancer indications. This dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications that demonstrated flat dose- and exposure efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the IB).
- Population PK analysis showed that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data that showed meaningful improvement in benefit-risk, including overall survival (OS) at 200 mg Q3W across multiple indications.
- Pharmacology data that showed full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumors (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W.

Among the eight randomized, dose-comparison studies, 2262 patients were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD -L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2; KN001 Cohort D; KN002; KN010; and KN021) and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3; KN001 Cohort F2; KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W dosages provided similar responses to the highest doses studied. Subsequently, flat-dose exposure-response relationships were also observed in other tumor types, including HNSCC, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data for pembrolizumab show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that a fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

Refer to the approved labeling and Investigator's Brochure for more details on Keytruda® (Pembrolizumab, MK-3475) (Keytruda Investigator's Brochure).

7.1.3. Selection of Doses in the study

Based on the cumulative PK, PD, and safety data in healthy volunteers (FLX475-01 Ph1 study), and in patients with advanced cancer (Phase 1 portion of the ongoing FLX475-02 Phase 1/2 study), a recommended Phase 2 dose of 100 mg QD for FLX475 in combination with standard dose pembrolizumab has been selected.

The dose of pembrolizumab used in this study, 200 mg as a 30-minute IV infusion Q3W, is the approved dosage in advanced cancer, based on clinical data from 8 randomized studies.

7.2. Overview of Treatments Administered

Subjects will take FLX475 orally once daily (QD) starting on Day 1 of Cycle 1 and in conjunction with pembrolizumab 200 mg by IV Q3W. Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting. Fasting is not required for FLX475 administration.

The treatments to be used in this study are outlined in Table 7.2:1.

Table 7.2:1 Study Treatments

Study Treatment	Formulation	Dose	Route of Administration	Sourcing
FLX475	Tablets	100mg, QD	Oral	Provided centrally by the Sponsor
Pembrolizumab	Solution for infusion	200 mg, Q3W	IV infusion	Provided centrally by the Sponsor

IV = intravenous, Q3W = once every 3 weeks, QD = once daily.

7.2.1. FLX475 Administration

FLX475 tablets are to be taken with water orally once a day at approximately the same time each day in every 3-week cycle (21 days) from Cycle 1 Day 1 onward. Fasting is not required for FLX475 administration. On days when a clinic visit, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed.

FLX475 should be taken approximately 1 hour before the pembrolizumab infusion, on days when pembrolizumab is also administered (i.e., Day 1 of each cycle).

The dose modification for FLX475 is provided in Section 7.3

7.2.2. Pembrolizumab Administration

Pembrolizumab 200 mg will be administered as an IV infusion over 30 minutes on Day 1 of every 3-week treatment cycle (i.e., every 21 days [±3 days]) after all procedures and assessments have been completed, and approximately 1 hour after the Day 1 dose of FLX475.

The site staff should make every effort to ensure that the infusion duration be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time of 25 to 40 minutes).

The Pharmacy Manual contains specific instructions for the preparation and administration of the pembrolizumab infusion.

7.3. Dose Modification

Dose modifications and drug discontinuation may be acceptable for toxicity but should be implemented at the investigator's discretion in consultation with the sponsor or medical monitor after considering the subject's condition and the clinical benefit to the subject of continuing treatment at the current dose.

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drug is required per the guidance below.

7.3.1. FLX475

For subjects receiving study treatment, the following dose modification and discontinuation guidelines must be followed:

- The investigator may interrupt treatment with FLX475 for any other AE considered unacceptable for the individual subject, and treatment may be resumed at the next lower dose level when resolved to Grade 0 or 1 or to pretreatment severity grade.
- If no lower dose level exists to which the subject may de-escalate, FLX475 should be discontinued.

Other dose modifications may be acceptable but should be implemented at the investigator's discretion in consultation with the medical monitor, considering the subject's condition and the clinical benefit to the subject of continuing treatment at the current dose.

If the subject requires a dose modification for an AE, then FLX475 administration should be interrupted, as necessary, until the AE resolves or stabilizes to an acceptable degree (generally to CTCAE(v5.0) Grade 0 or 1 or to pretreatment severity grade). Thereafter, treatment with FLX475 may be reinstituted at the next lower dose level. Subsequent reductions to successively lower dose levels can be made, if needed, as shown in Table **7.3:1** More frequent laboratory monitoring may be required.

Once the dose of study treatment has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the Sponsor or medical monitor's approval is required to increase the dose.

Table 7.3:1 Dose Modification Guidelines for FLX475-related Toxicity

Grade (CTCAE v5.0)	Treatment-Related Toxicity [a, b]			
	First occurrence	**Second occurrence** (same toxicity or new toxicity)	**Third occurrence** (same toxicity or new toxicity)	**Fourth occurrence**
Grade 1 or Tolerable Grade 2	Continue Treatment			
Intolerable Grade 2[c, d] or Grade 3[e, f]	◆ **Management:** Interrupt FLX475 until resolved to Grade 0-1 or tolerable Grade 2 (or baseline) ◆ **Dose Adjustment:** Reduce FLX475 dose by 1 level (75mg)	◆ **Management:** Interrupt FLX475 until resolved to Grade 0-1 or tolerable Grade 2 (or baseline) ◆ **Dose Adjustment:** Reduce FLX475 dose by lower level (50mg)	◆ **Management:** Interrupt FLX475 ◆ **Dose Adjustment:** Discuss with Sponsor (permanently discontinue from FLX475 treatment or to be in the subject's best interest to continue treatment, at a reduced dose)	N/A
Grade 4[g]	Discontinue Study Treatment			

Guide for Related Adverse Events					
Grade (CTCAE v5.0)		**First occurrence**	**Second occurrence** (same toxicity or new toxicity)	**Third occurrence** (same toxicity or new toxicity)	**Fourth occurrence**
Any drug-related AE (neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, cutaneous)	Grade 4	Permanently discontinue (Unless it is determined by the investigator, in consultation with the Sponsor or medical monitor, to be in the subject's best interest to continue treatment, at a reduced dose)			
Gastrointestinal (GI) tract	Grade 3	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at reduced dose: 100 mg → 75 mg	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at reduced dose: 75 mg → 50 mg	Permanently discontinue from FLX475 treatment	N/A
AST / ALT elevation or Increased bilirubin	Grade 3	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at the reduced dose: 100 mg → 75 mg	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at reduced dose: 75 mg → 50 mg	Permanently discontinue from FLX475 treatment	N/A

Guide for Related Adverse Events					
Grade (CTCAE v5.0)		**First occurrence**	**Second occurrence** (same toxicity or new toxicity)	**Third occurrence** (same toxicity or new toxicity)	**Fourth occurrence**
QTcF prolongation[h]	Grade 1	No dose reduction is required			
	Grade 2 (≤ 6 hours after FLX475 dose)				
	Grade 2 or 3 (immediately prior to or > 6 hours after FLX475 dose)	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at reduced dose: 100 mg → 50 mg	Permanently discontinued from FLX475 treatment (at 50 mg or lower dose level) or continue treatment either at 50 mg or at a reduced dose of 25 mg (If it is determined by the investigator, in consultation with the Sponsor or medical monitor, to be in the subject's best interest)	N/A	N/A

Guide for Related Adverse Events					
Grade (CTCAE v5.0)		**First occurrence**	**Second occurrence** (same toxicity or new toxicity)	**Third occurrence** (same toxicity or new toxicity)	**Fourth occurrence**
	Grade 3 (≤ 6 hours after FLX475 dose)	Withhold FLX475 treatment until AE Grade ≤1 (or to pretreatment severity grade) and then resume treatment at reduced dose: 100 mg → 50 mg	Permanently discontinued from FLX475 treatment (at 50 mg or lower dose level) or continue treatment either at 50 mg or at a reduced dose of 25 mg (If it is determined by the investigator, in consultation with the Sponsor or medical monitor, to be in the subject's best interest)	N/A	N/A
	Grade 4	Should be treated appropriately and permanently discontinued from FLX475 treatment (unless it is later determined by the investigator, in consultation with the Sponsor or medical monitor, to be in the subject's best interest to continue treatment)			

Note: For grading see CTCAE version 5.0. Collect all CTC grades of adverse events, decreasing and increasing grade.

BMI = body mass index, CTCAE = Common Terminology Criteria for Adverse Events.

a. An interruption of study treatment for more than 21 days will require Sponsor`s approval before treatment can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypothyroidism and/or diarrhea prior to any study treatment interruption or dose reduction.

c. Applicable only to Grade 2 toxicities judged by the subject or physician to be intolerable.
d. Obese subjects with weight loss do not need their weight to return to baseline weight or within 10% of baseline weight (i.e., Grade 1 weight loss). These subjects will restart the study treatment(s) at a lower dose once their weight remains stable for at least 1 week and they reach their normal BMI (if the weight loss occurs but is still above normal BMI, they can restart study treatment at a lower dose once their weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e. For Grade 3 toxicity, investigator will decide the probability of the event being related to 1 or both drugs and as to whether dose modification of either or both drugs is required.
f. For asymptomatic laboratory abnormalities, such as Grade ≥ 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.
g. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
h. Any subjects with observed QTcF prolongation of potential significance should have the ECG repeated for confirmation and electrolytes assessed and replaced as needed prior to action with study drug being taken. An average of QTcF values from triplicate ECGs and NOT an individual QTcF value from a single ECG should be used for dose modification considerations.

7.3.2. Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the final dose of pembrolizumab. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. Suspected irAEs should be adequately evaluated to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, Pembrolizumab should be withheld or permanently discontinued, and corticosteroids administered. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Criteria for dose delay, modification, or discontinuation of pembrolizumab are described below, and are based on criteria in the Keytruda Investigator's Brochure.

Table **7.3:2** shows treatment guidelines, including premedications, for subjects who experience an infusion reaction associated with the administration of pembrolizumab.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table **7.3:3** .

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, pembrolizumab is to be restarted within 3 weeks of the originally scheduled dose or within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the subject's eCRF.

Table 7.3:2 Infusion Reaction Treatment Guidelines for Pembrolizumab

CTCAE(v5.0) Grade	Treatment	Premedication for Subsequent Doses of Pembrolizumab
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

CTCAE(v5.0) Grade	Treatment	Premedication for Subsequent Doses of Pembrolizumab
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Table 7.3:3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
				consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST / ALT elevation or Increased bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d*]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitoring and Follow-up

AE(s)= adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. *If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

7.4. Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

FLX475 treatment must be discontinued but the subject should continue to be monitored in the study for any of the following reasons:

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section **7.3.1**.

Pembrolizumab treatment must be discontinued but the subject should continue to be monitored in the study for any of the following reasons:

- Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section **7.3.2**.

Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving [2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of FLX475] beyond the date when the initial CR was declared.

The reason for discontinuation of FLX475, pembrolizumab, or both will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Phase and complete protocol-specified End-of-Treatment and Follow-up visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will discontinue study treatment but agree to continue protocol-specified, post-treatment study visits, procedures, and survival follow-up, or whether the subject withdraws consent or is lost to follow-up. If a subject withdraws consent, the date will be documented in the source documents. Subjects may withdraw their consent for study participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the study. Furthermore, it may mean that further subject follow up on safety cannot occur. If subject want to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for study participation and explain the options for continued follow up after withdrawal. The investigator will complete the appropriate eCRF, indicating the primary reason for discontinuation. In addition, the date of final dose of study treatment(s) will be recorded on the appropriate eCRF.

All subjects who discontinue study treatment without having Progressive Disease (PD) will continue to undergo tumor assessments using the same imaging schedule used during the Treatment Phase (i.e., every 6 weeks (±7 days] in Year 1 or every 9 weeks (±7 days) in Year 2) until the start of a new anticancer therapy, disease progression, pregnancy, or the end of the study, whichever occurs first, unless the subject withdraws consent, is lost to follow up, or dies.

All subjects will be followed for survival until death, except for those subjects who withdraw consent or are lost to follow-up, or the Sponsor chooses to halt survival follow-up after completion of the primary study analysis.

7.5. Identity of Investigational Products

The study treatments under evaluation in this study are FLX475 and pembrolizumab. All study treatments will be provided to sites as open-label supplies by the Sponsor.

7.5.1. FLX475

[redacted] FLX475 will be supplied as tablets formulated with standard pharmaceutical-grade excipients designed to provide a release profile consisting of an immediate release of FLX475 drug substance over a period of approximately one hour.

[redacted]

7.5.2. Pembrolizumab

Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Pembrolizumab will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Pembrolizumab solution is provided in single-dose vials containing 100 mg/4 mL (25 mg/mL). Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution. An infusion of pembrolizumab in this study will require 2 vials of solution.

Refer to the latest Keytruda® Investigator's Brochure for complete details.

7.5.3. Supply, Packaging, and Labeling of Study Drug

FLX475 and pembrolizumab will be provided to the investigational sites by the Sponsor.

FLX475 for oral administration will be provided as tablets containing the active ingredient as well as standard pharmaceutical grade excipients. FLX475 will be packaged in individual bottles with study-specific labeling.

Pembrolizumab will be supplied in study-specific labeled vials packaged in individual cartons with study-specific labeling.

All study treatments will be labeled in accordance with text that is in full compliance with the requirements for each participating country and is translated into the required language(s) for each of those countries.

7.5.4. Storage Conditions

Bottles containing tablets of FLX475 should be stored at a controlled room temperature, 20~25℃ (68–77℉), excursions permitted 15~30℃ (59–86℉). Study drug should be stored in the container in which it is supplied, in a secured area to which access is limited to appropriate study personnel. FLX475 tablets should be stored protected from light and according to the storage information provided on the label.

For vial containing pembrolizumab, store vials under refrigeration at 2~8℃ (36~46℉) in original carton to protect from light. Do not freeze and do not shake.

Note: According to Korean Pharmacopoeia (KP), the room temperature is defined as 1~30℃.

7.5.5. Drug Accountability

FLX475 will be self-administered in this study. On Day 1 of each cycle, FLX475 will be self-administered in the clinic. After a new supply of study treatment has been dispensed for that cycle, a diary card will be provided to each subject to record all dose administration information at home for drug accountability purposes.

The disposition of all FLX475 and pembrolizumab supplies should be documented from the time of receipt at the site through subject dispensing and return. The investigator and the site staff (or if required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study treatments/study supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to GCP guidelines as well as local requirements.

Under no circumstances will the investigator allow the study treatments to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study treatments, dispensing of study treatments to the subject, collection and reconciliation of unused study treatments that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study treatments to the Sponsor or designee or (where applicable) destruction of reconciled study treatments at the site. This includes but may not be limited to: (a) documentation of receipt of study treatments, (b) study treatments dispensing/return reconciliation log, (c) study treatments accountability log, (d) all shipping receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction or equivalent documentation of study treatments that occurs at the site. All forms will be provided by the Sponsor or designee.

The study treatments and inventory records must be made available, upon request, for inspection by a designated representative of the Sponsor or a representative of a health authority (e.g., FDA, MFDS). As applicable, all unused study treatments and used study treatments are to be returned to the investigator (or if required, the head of the medical institution or the designated pharmacist) by the subject Unused study treatments that were shipped to the site but not dispensed to subjects, requests to ship the returned and unused study treatments to the Sponsor's designated depot. Site destruction Standard Operating Procedures (SOPs) must be reviewed and confirmed by Sponsor to ensure proper destruction will occur. Upon completion of drug accountability and reconciliation procedures by the site's staff and documentation procedures by the Sponsor's personnel, study treatments that are to be returned to the Sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. Where study treatments are approved for destruction at the site, destruction will occur following the site's standard operating procedures and certificates of destruction or equivalent documentation of destruction will be provided to the Sponsor.

Drug accountability will be reviewed by Sponsor representatives during site visits and at the completion of the study. For details on destruction documents, please see the Pharmacy Manual.

7.5.6. Study Treatment Compliance

FLX475 tablets will be self-administered by participating study subjects. Subjects will be provided with dosing instructions at the start of their participation in the study and at the time of any dosing modifications (e.g., dose reduction due to AE), and will be encouraged by site staff to take the study medication according to the instructions for the duration of the study. A diary card will be provided for subjects to record their adherence to the oral medication, which will be reviewed by qualified site staff during study visits. Subjects will be instructed to bring the assigned boxes of study medication to the site staff at each study visit, whether empty or not. At the completion of each treatment cycle and at other times when the study drug dispensed might be returned (e.g., in the case of a dose reduction), the returned study medication will be checked for any unused study drug, and a tablet count will be performed for any remaining study medication. This information will be recorded electronically for each treatment cycle.

Any events of non-compliance to the protocol will be documented in the source document and e-CRF.

7.6. Prior and Concomitant Therapy

7.6.1. Recording of Prior and Concomitant Treatments and Procedures

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medications taken by the subject within 30 days prior to screening. Prior antibiotic usage (name, dose, and duration) for up to 6 months prior to screening should also be recorded, if the information is readily available.

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All prior medications (including over-the-counter medications) administered within 30 days prior to screening and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study treatment will be recorded on the appropriate eCRF(s). Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with the study treatment may be continued during the study. If the concomitant medication/therapy is being administered for a medical condition present at the time of enrollment the study, the investigator will record the medical condition on the appropriate eCRF.

7.6.2. Drug-Drug Interactions

[redacted]

No formal PK drug interaction studies have been conducted between FLX475 and pembrolizumab. Pembrolizumab is a monoclonal antibody; PK interactions with FLX475 (and vice versa) are not expected.

Refer to the prescribing information for the most current information for drug-drug interaction studies conducted with pembrolizumab.

7.6.3. Permitted Concomitant Therapies

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, antidiarrheal drugs, etc.) of complications or AEs, or therapy to ameliorate symptoms, may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study treatment.

Any additional procedural or subject-specific particularities should be discussed with the Sponsor.

7.6.4. Prohibited Concomitant Therapies and Drugs

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during this trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation of study treatment or vaccination may be required. The investigator should discuss any

questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination is at the discretion of the investigator. However, the decision to allow the subject to continue to receive study treatment requires the mutual agreement of the investigator, the Sponsor, and the subject. (See Appendix **6**)

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or FLX475
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary non-target lesion or to the brain may be allowed at the investigator's discretion.

- Live or live attenuated vaccines within 30 days prior to the first study dose and during participation in the study.

  Note: Killed vaccines are allowed.

- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for COPD exacerbations
  - For chronic systemic replacement not to exceed 10mg/day prednisone equivalent
  - In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

  The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Inhaled steroids are allowed for management of asthma or seasonal allergies. The use of prophylactic corticosteroids to prevent allergic reactions (e.g., IV contrast dye or transfusions) is permitted

If the investigator determines that a subject requires any of the aforementioned treatments for any reason, study intervention FLX475 and pembrolizumab must be discontinued. If a subject receives additional anticancer therapies, this will be judged to represent evidence of Progressive Disease (PD), and study treatment will be discontinued. These subjects should complete all End-of-Treatment assessments and continue to be followed for survival in the Follow-up Phase unless they withdraw consent or are lost to follow-up.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications administered during SAEs or events of clinical interest (ECIs) are to be recorded on a SAE form. SAEs and ECIs are defined in Section **9.2.2.**

7.6.5. Rescue Medication and Supportive Care

Subjects should receive appropriate supportive care measures for an AE as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section **7.3.1**. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

Note: If, after evaluation, the event is determined to be not related to pembrolizumab (or FLX475), the investigator does not need to follow the treatment guidance.

8. STUDY PROCEDURES AND ASSESSMENTS

8.1. Pretreatment Period

8.1.1. Screening Period

Screening will occur from Day -30 to Day -1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Re-screening is allowed after discussion with the medical monitor. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Once signed informed consent is obtained, planned procedures and evaluations will be performed/recorded. Procedures to be followed when obtaining informed consent are detailed in Section **13.2**.

Subjects must have measurable disease according to RECIST 1.1 as defined in Eligibility Criteria. Subjects who successfully complete the screening process will be enrolled for the study and start study treatment within 30 days of initial screening. If judged to be ineligible, the reason(s) for screening failure will be described in the "Subject Screening Log" to the extent possible.

See the Schedules of Assessments (Table **1.2:1**) for a complete list of Screening assessments.

- Informed Consent
- Inclusion/Exclusion Criteria confirmation
- Demographics/Baseline characteristics
- Physical examination, including height, weight, ECOG PS, and vital sign measurements
- Prior and concomitant drugs/therapy
- Triplicate 12-Lead ECG, ECHO/MUGA scan
- Blood, urine and tissue for laboratory tests and biomarkers, as indicated on Table **1.2:1**
- Serum pregnancy test on all female subjects unless Menopausal has been diagnosed
- Tumor Imaging/Staging (CT/MRI Scan) (collected data could be used if the data was collected within 30 days before start of study treatment)
- Adverse events/Serious adverse events assessment

8.1.1.1. Demographics/ Baseline characteristics

Demography information will include Year of Birth (or age), sex, and race.

Baseline characteristics will include ECOG PS (Appendix **3**), NYHA cardiac disease classification (Appendix **4**), and cancer staging at the time of initial diagnosis. The subjects' medical and surgical histories, including those for their underlying cancer, will be obtained during the Screening Phase, along with a record of prior and concomitant medications.

Note: For medical and surgical histories, all clinically significant medical conditions or surgeries occurred within the last 5 years and prior to signing the main informed consent will be recorded. Information related to prior cancer history, prior cancer therapy and procedures related to target indication of the study will be collected without limitation of timeframe.

8.1.1.2. Laboratory test

Laboratory screening tests (Serum chemistry, Hematology, coagulation test, Urinalysis, Pregnancy test, Thyroid function test) should be performed within 14 calendar days prior to the first study dose at screening visit.

8.1.1.3. Assessment of AE/SAE

Assessment of AE/SAE after the consent form is signed will be performed in order to obtain basic information required to determine a potential association between the study drug and adverse events. Safety will be rated based on assessments of clinical and/or laboratory toxicities and signs per NCI-CTCAE v5.0.

8.1.1.4. Collection of samples

8.1.2. Method of Treatment Assignment

Subjects may be eligible to enroll once all screening assessments and procedures are completed and results indicate that all eligibility criteria are met.

Enrollment of a subject into the study will be performed according to the following procedure.

- Subjects with an EBV-positive result from local test or documents can be enrolled, but confirmation tests should be performed at the central laboratory, and the final EBV test result judgment are based on the results of the central laboratory.
- Upon completion of all screening evaluations and verification, the site eligibility packet will be forwarded to Medical monitor and Sponsor for approval to enroll the subject.
- Once eligibility is confirmed and the subject is approved for enrollment, the subject number, cohort assignment will be assigned via the IWRS.

8.1.3. Baseline Period

Baseline assessments must be performed on Cycle 1 Day 1 prior to administration of the first study dose.

The following assessments will be performed on Cycle 1 Day 1 prior to the first study dose:

- Concomitant drugs/therapy
- Physical examination and ECOG PS
- Vital sign measurements
- Triplicate 12-Lead ECG
- Blood and urine samples for laboratory tests and serum biomarkers as indicated on Table **1.1:1**
- Pregnancy test on all subjects unless Menopausal has been diagnosed
- Pharmacokinetics assessments
- Adverse events assessment

8.1.3.1. 12-Lead ECG

The 12-Lead ECG will be performed in triplicate in supine position. (3 separate ECGs approximately 2 minutes apart; 10 minutes resting prior to first ECG)

ECG will precede pharmacokinetic blood sample if they are to be overlapped.

8.1.3.2. Laboratory test

Baseline laboratory tests (Serum chemistry, Hematology, coagulation test, Urinalysis, Pregnancy test, Thyroid function test) should be performed pre-dose at study visit.

8.2. Treatment Period

The Treatment Period for each subject will begin at the start of dosing and will end with the completion of the End-of-Treatment Visit.

The following conditions apply:

- Subjects will receive study treatment with FLX475 and pembrolizumab as continuous 3-week (21-day) cycles. Treatment cycles will be counted continuously regardless of dose interruptions (assessments corresponding to each cycle should be performed regardless of study drug administration).
- Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table **1.2:1**)
- Subjects will continue to receive study treatment for a maximum of 35 cycles (approximately 2 years) or until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification and supportive treatment, the development of intercurrent illness that precludes continued study treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first.
- Subjects who discontinue pembrolizumab due to toxicity may continue treatment with FLX475 alone only if it is determined to be in the subjects' best interest and upon agreement with the medical monitor.

- Subjects who discontinue FLX475 due to toxicity may continue treatment with pembrolizumab alone only if it is determined to be in the subjects' best interest and upon agreement with the medical monitor.
- Discontinuation of treatment may be considered for those subjects who fulfill all of the following criteria: attain a confirmed CR, have been treated for at least 8 cycles (≥ 24 weeks) with pembrolizumab, and have received at least 2 infusions of pembrolizumab and at least 80% of the planned doses of FLX475 beyond the date when the initial CR is declared.
- In the presence of clinical benefit, subjects who complete treatment with pembrolizumab may continue to receive FLX475 alone after this time point if it is determined to be in the subject's best interest by the investigator in consultation with the Sponsor.

For subjects who have radiological Progressive Disease (PD) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by the investigator, the investigator will decide whether the subject can continue to receive study treatment until repeat, confirmatory imaging is obtained using modified RECIST for immunotherapies (iRECIST) for subject management (see Appendix **5** for details). The investigator's decision is based on the subject's overall clinical condition.

8.3. End of Treatment Period

A subject may elect to discontinue treatment or withdraw consent from the study at any time for any reason. This will mean that no further information may be collected for the purpose of the study. Furthermore, it may mean that further subject follow-up on safety cannot occur. If a subject want to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for study participation and explain the options for continued follow up after withdrawal. If obtain the subject's agrees to further follow up, the subject will undergo the procedures for the EOT visit and follow up as outlined the Schedule of Procedures/Assessments (Table **1.2:1**).

Unless subjects withdraw consent or are lost to follow-up, all subjects who discontinue study treatment prior to Progressive Disease (PD) will undergo tumor imaging at the time of treatment discontinuation (± 4-week window). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

Subject will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

The investigator will promptly explain to the subject involved that study treatment and procedures will be discontinued for that subject, and appropriate medical treatment and other necessary measures will be provided.

Subjects who consent to follow-up will be monitored for disease progression and/or survival.

Study disposition information will be collected on the appropriate eCRF. Subjects who withdraw early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, progression of disease, withdrawal of consent, pregnancy, study terminated by Sponsor, or other.

8.4. Follow-up Period

Subjects will undergo assessments as defined in the Schedule of Procedures/Assessments (Table **1.2:1** Table 1.2:1).

8.4.1. Initial Follow-up

Unless subjects withdraw consent or are lost to follow-up, subjects who discontinue study treatment will be followed for acquisition of safety information for 30 days (+7 days) after the final dose of study treatment. All AEs that occur prior to the Initial Follow-up Visit should be recorded. AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first.

8.4.2. Initial Follow-up Visit

Subject who followed Initial Follow-up period should be assessed ECGs and PK sampling on 30 days (+7 days) after the final dose of study treatment. The 12-Lead ECG will be performed in triplicate and ECG matched PK sampling will also be obtained for safety monitoring of subject. (3 separate ECGs approximately 2 minutes apart; 10 minutes resting prior to first ECG)

8.4.3. Long-term Follow-up

All subjects who discontinue study drug will be followed for survival and any post-study anticancer treatment via at least every 3 months (± 7 days). Long-term follow up information will be collected during routine clinic visits, other site contact with the subjects, or via telephone or e-mail with the subject/caregiver or referring physician's office. These data will be collected in the source documents (e.g., subject medical record) and recorded onto a specific eCRF. The Sponsor may choose to discontinue survival follow-up following completion of the primary study analysis when appropriate, e.g., when only a minimal number of subjects remain in follow up.

If a subject becomes unavailable for follow-up (e.g., misses scheduled assessment, telephone contact), the investigator or designee will make every attempt to contact the subject to determine his or her status. All attempts at contact will be recorded in the subject's medical records. A subject may be considered lost to follow-up after a minimum of two attempts to contact the subject (e.g. by email or telephone) have been unsuccessful.

Serious adverse events will be collected through 90 days following cessation of study treatment, or 30 days after final dose if the subject initiates new anticancer therapy, whichever occurs first.

For subjects who discontinue study treatment without documented Progressive Disease (PD), every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used during study treatment (every 6 weeks ±1 week in Year 1 or every 9 weeks ± 1 week in Year 2) until the start of a new anticancer therapy, Progressive Disease (PD), pregnancy, death, withdrawal of consent, loss to follow-up, or termination of the study, whichever occurs first.

For subjects who discontinue study treatment due to documented PD, no tumor imaging is required during follow-up if the investigator elects not to implement iRECIST.

8.5. Unscheduled Visit

In addition to regular study visits, an unscheduled visit can be placed during the study as required, for example, if adverse event, such as cardiac dysfunction or elevation of hepatic enzymes is suspected, or further tests are needed for follow-up of the AEs. For this, the investigator will inform subjects of this during regular study visits and instruct them to have a contact the investigator immediately if they have experienced AEs. The corresponding visits must be recorded in both eCRF and source documents.

9. TYPES OF ASSESSMENT

9.1. Efficacy Assessments

9.1.1. Tumor Imaging and Disease Assessment

RECIST 1.1 will be used as the primary measure for assessment of tumor response and progression, date of Progressive Disease (PD), and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment).

Investigator-determined response assessments will be performed at each assessment time point and recorded on the eCRF. The assessments for tumor progression may also be performed by the investigator using iRECIST after the first radiologic evidence of Progressive Disease (PD) by RECIST 1.1.; While awaiting confirmatory tumor imaging by site by iRECIST, the study treatment may continue at the investigator's discretion based on the clinically stable/unstable condition of the subject (Appendix **5**).

CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan should be used consistently for each subject across all time points throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Note: for the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site or the radiological reviewer located at the site or at an offsite facility.

- In general, imaging should include the chest (CT), and abdomen and pelvis (CT or MRI)
- Imaging should include other known or suspected sites of disease
- If brain scans are performed, magnetic resonance scans are preferred. However, CT scans are acceptable, if MRI is medically contraindicated. The brain scan (MRI pre- and postgadolinium or CT with contrast) will be performed at Screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a CR. For subjects with a history of protocol-eligible, treated brain metastases, a brain scan will be required at all tumor assessment time points.

9.1.2. Timing of Tumor Imaging

9.1.2.1. Screening

Initial tumor imaging at Screening must be performed within 30 days prior to Cycle 1, Day 1. The investigator must review screening images to confirm that the subject has measurable disease per RECIST 1.1. Historical CT or MRI scans performed within 30 days before the start of study treatment, may be used as screening scans, provided they meet minimum standards. The image will be sent to central imaging for further analysis.

Confirmation of measurable disease based on RECIST 1.1 using local assessment at Screening will be used to determine subject eligibility.

9.1.2.2. During Treatment

All images during treatment will be sent to central imaging for further analysis. The first imaging assessment during study treatment should be performed 6 weeks (±7 days) from Cycle 1, Day 1.

Subsequent tumor imaging should be performed every 6 weeks (±7 days) or more frequently if clinically indicated for the first year of treatment. After 1 year, subjects who continue to receive study treatment will have imaging performed every 9 weeks (±7 days) for up to 1 additional year.

The timing of tumor imaging should follow calendar days and should not be adjusted for delays in cycle starts. Tumor imaging should continue to be performed until Progressive Disease (PD) is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer therapy, withdrawal of consent, loss to follow-up, death, 2 years of study treatment, or termination of the study by the Sponsor, whichever occurs first.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Subjects will then return to regularly scheduled imaging, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

[redacted]

Per iRECIST, investigator-assessed Progressive Disease (PD) in the clinically stable subjects should be confirmed by the investigator 4 to 8 weeks after the first radiologic evidence of Progressive Disease (PD). A subject with unconfirmed Progressive Disease may continue to receive study treatment at the discretion of the investigator until progression is confirmed by the investigator, provided the subject has met the conditions detailed in Section **9.1.3**. Subjects who have confirmatory imaging do not need to undergo the next scheduled tumor imaging assessment if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable.

Subjects who have confirmed Progressive Disease (PD) by iRECIST, as assessed by the investigator, will discontinue study treatment. Exceptions are detailed in Section **9.1.3**.

9.1.2.3. End of Treatment and Follow-up Tumor Imaging

Subjects who discontinue study treatment for a reason other than Progressive Disease (PD), tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was performed within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue study treatment due to documented Progressive Disease (PD), this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For subjects who discontinue study treatment without documented Progressive Disease (PD), every effort should be made to continue monitoring disease status during the Follow-up Phase by tumor imaging using the same imaging schedule used during the Treatment Phase (i.e., every 6 weeks ±7 days for the first year and every 9 weeks ±7 days in the second year) until the start of a new anticancer therapy, Progressive Disease, pregnancy, death, withdrawal of consent, loss to follow-up, or termination of the study, whichever occurs first. The image will be sent to central imaging for further analysis.

9.1.3. Disease Assessment by iRECIST

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess solid tumor response and progression, and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the investigator, in conjunction with the local radiologist, according to the rules outlined in Appendix **5**.

This allowance to continue treatment despite initial radiologic Progressive Disease (PD) takes into account the observation that some subjects can have a transient tumor flare after the start of immunotherapy, then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed clinically unstable should discontinue study treatment at first radiologic evidence of Progressive Disease (PD) as assessed by the investigator, and is not required to have repeat tumor imaging for confirmation of Progressive Disease (PD) by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm Progressive Disease (PD) by iRECIST, per investigator assessment.

If repeat imaging does not confirm Progressive Disease (PD) per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If Progressive Disease (PD) is confirmed, subjects will be discontinued from study treatment.

If a subject has immune confirmed progressive disease (iCPD) as defined in Appendix **5**, study treatment should be discontinued.

A description of the adaptations and iRECIST process is provided in Appendix **5**, with additional details in the iRECIST publication [**16**]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table in Appendix **5**.

9.2. Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs and SAEs using CTCAE v5.0 (Appendix **2**), regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations and vital sign measurements; and periodic ECGs.

9.2.1. Adverse Events and Events of Clinical Interest (AEs and ECIs)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. For this study, the study treatments are FLX475 and pembrolizumab. An AE does not necessarily have a causal relationship with the medicinal product. Progression of the cancer under study is not considered an AE.

AEs, SAEs, and other reportable safety events must be reported to the investigator by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).

- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as Progressive Disease (PD) rather than as an AE.
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or radiograph) that results in symptoms, a change in treatment, or discontinuation of study treatment
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality is assessed as clinically significant by the investigator, or leads to any type of intervention, withdrawal of study treatment, or withholding of study treatment, whether prescribed in the protocol or not

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE, as well as other reportable safety events (e.g., pregnancy). Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the average QTcF interval is ≥ 450 ms or there is an average increase of more than 60 ms from baseline (defined as average QTcF value from C1D1 pre-dose ECGs). Any ECG abnormality that the investigator considers as an AE should be reported as such.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

All AEs observed during the study will be reported on the eCRF. All AEs, SAEs, and other reportable safety events that occur after the consent form is signed must be reported by the investigator. Other events that occur prior to the consent form is signed should be recorded as medical history.

All AEs or events of clinical interest (ECIs) that occur after the consent form is signed through 30 days following cessation of study treatment must be reported on the eCRF by the investigator. See Section **9.2.2** for further discussion of SAEs and ECIs.

All AEs must be recorded and followed through 30 days following cessation of study treatment (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

9.2.1.1. Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v5.0 (Appendix **2**). Investigators will report CTCAE(v5.0) grades for all AEs (for both increasing and decreasing severity).

9.2.1.2. Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event

9.2.1.3. Binary causality

The relationship of each AE to the study treatment will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study treatment caused the AE?

Not Related

- A causal relationship between the study treatment and the AE is not a reasonable possibility.

Related

- Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but probably the result of another factor; not clearly the result of an external factor, or
- Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug but possibly the result of another factor; not clearly the result of another factor, disappears or decreases after discontinuation of the study drug, or
- Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug, not the result of another factor, disappears or decreases after discontinuation of the study drug, and recurs on re-challenge (if restarted).

9.2.2. Serious Adverse Events, Events of Clinical Interest, and Events Associated with Special Situations

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events of clinical interest (ECIs) in this study, whether serious or not, include:

1. An overdose of FLX475 or pembrolizumab, as defined in Section **9.2.3**, Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT value that is ≥ 3 times the upper limit of normal (×ULN) and an elevated total bilirubin value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase value that is < 2 × ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing.*

   **Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor or medical monitor. However, abnormalities of liver blood test values that do not meet the criteria noted above are not ECIs for this study.*

3. QTcF interval ≥ 450 ms or a > 60 ms increase from baseline (defined as average QTcF value from C1D1 pre-dose ECGs).
4. Significant GI toxicity, e.g., nausea, vomiting, diarrhea, or constipation not easily managed with symptomatic medications in an outpatient setting.

In addition to the above ECIs, Events Associated with Special Situations include pregnancy or exposure to study treatment through breastfeeding; AEs associated with study treatment overdose, or medication error. Events associated with special situations and ECIs are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All ECIs and AEs associated with special situations are to be reported on a completed SAE form by email or fax whether or not they meet the criteria for SAEs, and are subject to the same reporting timelines described in Section **10.1.1**.

Serious adverse events must be reported after the consent form is signed through 90 days following cessation of study treatment, or 30 days after final dose if the subject initiates new anticancer therapy, whichever occurs first.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study treatment administration)

- Hospitalization for administration of study treatment or insertion of access for administration of study treatment
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study enrollment

If possible, blood sample(s) for the measurement of FLX475 and pembrolizumab plasma concentrations should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution. See Section **10.1.1** for SAE reporting requirement.

9.2.3. Overdose

For this study, an overdose of FLX475 will be defined as any dose ≥ 2 times the indicated dose. An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater the indicated dose. No specific information is available on the treatment of an overdose of FLX475 or pembrolizumab. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.2.4. Pregnancy, Contraception, and Breastfeeding

FLX475 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if FLX475 or pembrolizumab has transient adverse effects on the composition of sperm.

Subjects should be informed that taking the study drug(s) may involve unknown risks to the unborn baby if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (from the start of study treatment [or 14 days prior to the first study dose for oral contraception] throughout the study period up to at least 120 days after the final dose of study treatment). If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a female subject inadvertently becomes pregnant while receiving treatment with FLX475, pembrolizumab or both, she must immediately discontinue study treatment. If a female partner of a male subject inadvertently becomes pregnant while the subject is receiving treatment with FLX475, pembrolizumab, or both, the investigator must be informed immediately. The investigator will contact the subject at least monthly and document the status of the mother and pregnancy until the pregnancy has been completed or terminated (spontaneously or through induced abortion). See Section **10.1.2** for Pregnancy and Breastfeeding reporting requirement.

It is unknown whether FLX475 or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions of drugs in the nursing infant, females who are breastfeeding are not eligible for enrollment in this study.

9.2.5. Clinical Safety Laboratory Assessments

Clinical laboratory tests to be performed are summarized in Table **1.2:1** . Subjects should be in a seated or supine position during blood collection. The Schedules of Procedures/Assessments show the visits and time points at which blood, urine for clinical laboratory testing will be collected in the study. All tests will be performed at a local laboratory at the investigator site.

Table 9.2:1 Laboratory tests

Category	Parameters
Hematology	CBC and Differential (WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential)
Coagulation	PT, PTT or aPTT and INR
Serum Chemistry	-
- Electrolytes	sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous
- Liver function tests	total bilirubin, ALP, AST, ALT
- Renal function tests	BUN, creatinine (or CrCl)
- Thyroid function tests	Triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH)
- Other	Albumin, glucose[a], lactate dehydrogenase, total protein, uric acid, amylase, lipase, Pregnancy test (serum or urine)[b]
Urinalysis	Specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).

a. For subjects with blood glucose >ULN at screening or clinically significant elevations on study (e.g. potentially considered an AE), a fasting (>6 h, water only) blood glucose sample should be obtained within 24 hours or as feasible
b. Females of childbearing potential. Only serum pregnancy test at screening

Results from all hematology, clinical chemistry (including serum pregnancy test, as applicable), or urinalysis samples (including urine pregnancy test, as applicable) obtained prior to study treatment administration should be reviewed prior to administration/dispensing of study treatment at the beginning of Cycle 1, at the investigator's discretion, and upon request of the Sponsor (e.g. due to borderline or abnormal values at screening).

9.2.6. Vital Signs and Weight Measurements

Blood pressure, pulse rate, respiratory rate and body temperature will be taken with the subject in a sitting position.

Vital signs will be performed at the time points specified in table below.

Table 9.2:2 Vital sign time per visit

Visit	[redacted]
Screening [b]	[redacted]
Cycle 1 Day 1	[redacted]
Cycle 1 Day 8, 15	[redacted]
Cycle 2 Day 1	[redacted]
Cycle 2 Day 8, 15	[redacted]
Cycle 3 Day 1, 15	[redacted]
Day 1 of Cycle 4 and subsequent cycles	[redacted]
ED/EOT	[redacted]

a. Time points for 0 hour: pre-dose, within 30minutes prior to administration
b. It will be performed at screening visit regardless of time

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedules of Procedures/Assessments (Table 1.2:1) by a validated method. Blood pressure and pulse rate will be measured with the subject in the sitting position, after resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for subjects with systolic BP < 140 mmHg and diastolic BP < 90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (i.e., the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

9.2.7. Physical Examinations / ECOG PS

Physical examinations (including a neurologic examination) will be performed as designated in the Schedules of Procedures/Assessments (Table 1.2:1). Documentation of the physical examination will be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF. A symptom-directed physical examination will be performed as clinically indicated.

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, a complete neurological examination and other body system. Height (only at screening visit) and weight will be taken.

After signing of informed consent, significant findings present during the screening will be recorded on the appropriate eCRF. Changes from Screening in physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Performance status will be evaluated per Eastern Cooperative Oncology Group (ECOG) scale.

9.2.8. Electrocardiograms

The 12-Lead ECG will be performed in triplicate in supine position. (3 separate ECGs approximately 2 minutes apart; 10 minutes resting prior to first ECG) ECG will precede blood sample if they are to be overlapped.

Triple 12-lead ECGs will be performed at the time points specified in table below (note that designated "Pre-dose" ECGs should be obtained at study visits even when study treatment is being held / not given).

Table 9.2:3 Triple 12-Lead ECGs time per visit

Visit	[redacted]
Screening [c]	[redacted]
Cycle 1 Day 1	[redacted]
Cycle 1 Day 8, 15	[redacted]
Cycle 2 Day 1	[redacted]
Cycle 2 Day 8, 15	[redacted]
Day 1 of Cycle 3 and subsequent cycles	[redacted]
ED/EOT	[redacted]
Initial Follow-up [c]	[redacted]

a. Time points for 0 hour: pre-dose, within 30 minutes prior to administration
b. If done in parallel with blood sampling, perform prior to blood sampling
c. It will be performed at screening visit or the Initial Follow-up Visit regardless of time

ECGs will be recorded and evaluated at the clinical study (local) site for the purposes of real-time cardiac safety monitoring for individual subjects and will be collected, stored and analyzed subsequently at a designated central facility.

Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 x 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Data should be collected using digital machines and electronically archived. Subjects must remain undisturbed in the supine position for a period of ≥ 10 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in Section 9.2.1 of this protocol and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF. ECG will precede blood sample if they are to be overlapped.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

9.4. Biomarkers

Biomarker study will be performed in this study as described below. Sampling, processing, storage and shipment of instructions will be provided in the lab manual. Please refer to the lab manual for more detailed information. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory.

Results of studies for biomarker will be reported separately and not be included in the clinical study report.

[redacted]

Tissue samples should be undergone a process of being fixed in FFPE block and shipped to sponsor designated analytical laboratory at room temperature. Detailed procedure will be described in lab manual for shipping and storage for analysis.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. SAFETY MONITORING AND REPORTING

10.1. Reporting of Adverse Events

10.1.1. Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported to the Sponsor or designee on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Regardless of treatment arm, all SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by his/her institution. A copy of this communication must be forwarded to the Sponsor or designee for filing in the Sponsor's Trial Master File.

10.1.2. Reporting of Pregnancy and Breastfeeding

Any female subject who becomes pregnant must be withdrawn from the study.

Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the final dose of study treatment or 30 days following the final dose of study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported to the Sponsor or designee. Also, any exposure of an infant to study treatment through breastfeeding during study treatment or within 120 days of the final dose of study treatment, or 30 days following the final dose of study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported to the Sponsor or designee.

Regardless of study treatment agent, if an adverse outcome of a pregnancy is suspected to be related to study treatment exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section **10.1.1**, Reporting of Serious Adverse Events,).

Pregnancies or exposure of an infant to study treatment through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the time that the investigator becomes aware of the pregnancy. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the time that the investigator becomes aware of the outcome, if the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

10.1.3. Reporting of Events Associated with Special Situations

10.1.3.1. Reporting of Adverse Events Associated with Study Drug Overdose, or Medication Error

An overdose or medication error is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or medication error should be recorded on the Adverse Event eCRF. Whether or not the associated adverse event fulfills the seriousness criteria, the event should be reported to the Sponsor on a completed SAE form by email or fax immediately (no later than 24 hours from when the investigator becomes aware of the event; see Section **10.1.1** for reporting instructions.)

10.1.4. Expedited Reporting

The Sponsor must inform investigators (or as required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

10.1.5. Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or designee to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local and regional requirements.

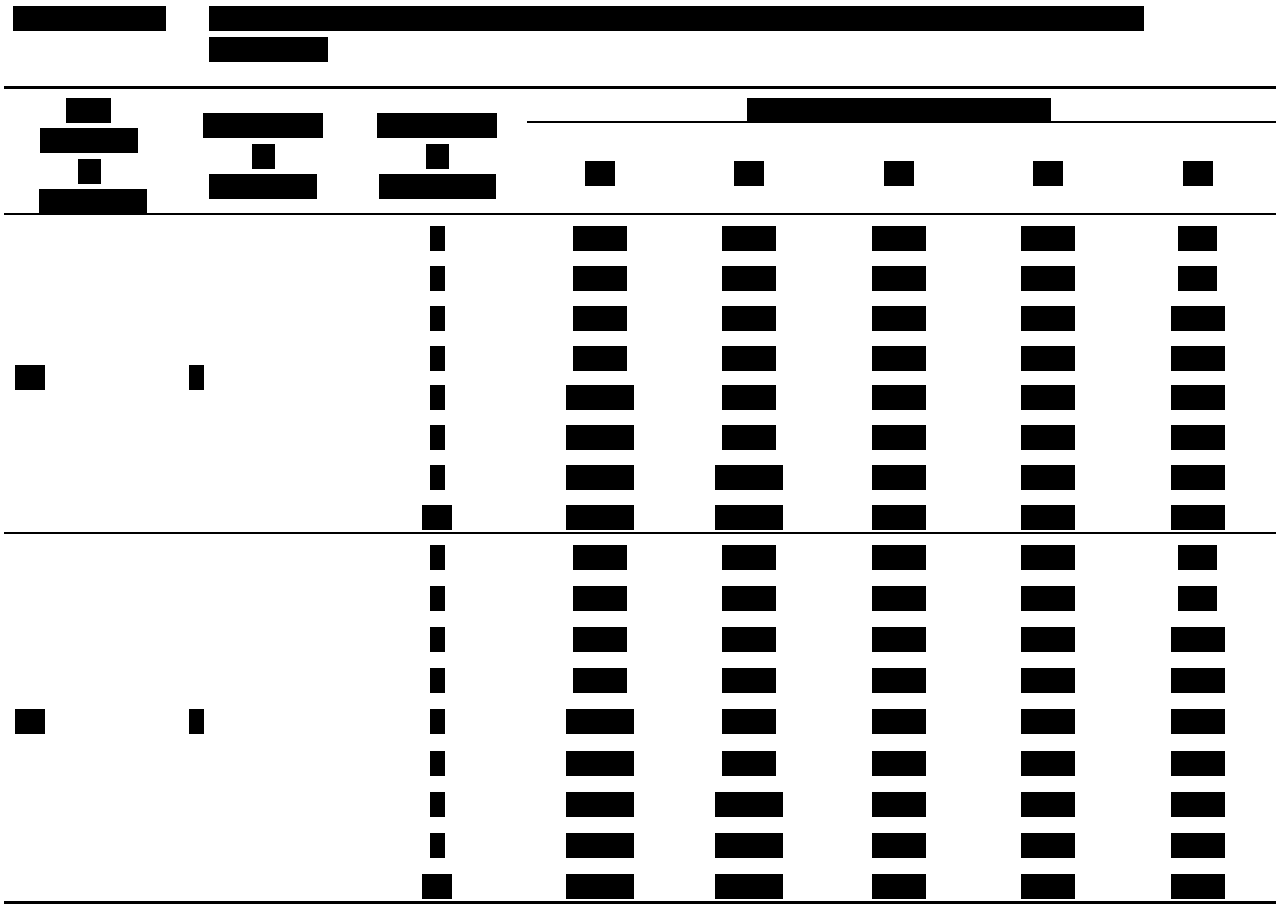
11. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

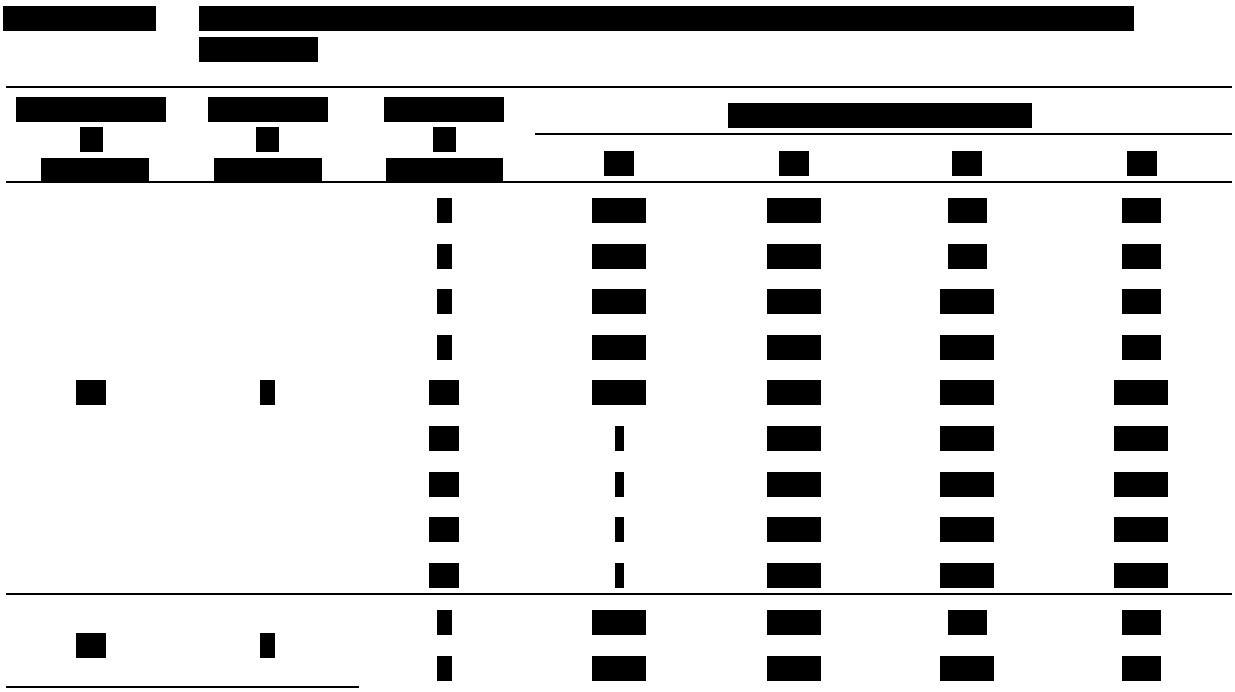
11.1. Sample Size Determination

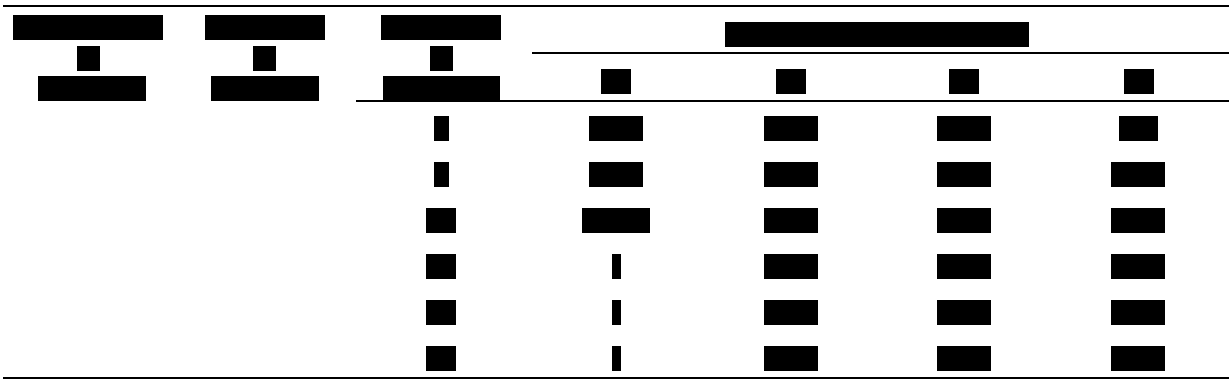
There is little known about the objective response rate from the subjects who have progressed on at least 2 prior systemic treatments for advanced or metastatic gastric cancer excluding check point inhibitor (CPI). In addition, considering the study nature to explore the safety and efficacy by FLX475 and pembrolizumab, no formal statistical testing will be done. As stated in the study design part, each cohort will enroll target subjects separately and both cohorts will initiate 2-stage design. The initial number of target subjects for the 1st stage for both cohorts is determined as 10 based on feasibility. However, the target subject number for the 2nd stage would be determined based on the overall safety assessment and the posterior probability of at least 80% to achieve the ORR ≥ 15% and ORR ≥ 30% for cohort 1 and cohort 2, respectively.

The posterior probability for ORR ≥ 15% and ORR ≥ 30% for cohort 1 and 2, respectively, based on the responses in the first and second stage is described in the Table **11.1:1** and Table **11.1:2** below assuming uniform prior distribution for ORR. For example, if we observed 1 response out of the initial 10 subjects of cohort 1 at 1st stage followed by 6 responses out of additional 20 subjects at 2nd stage, we could assume that the probability of ORR ≥ 15% by FLX475 and pembrolizumab combination therapy would be 92% based on the observed data (Table **11.1:1**). Also, if we observed 1 response out of the initial 10 subjects of cohort 2 at 1st stage followed by 7 responses out of additional 10 subjects at 2nd stage, we could assume that the probability of ORR ≥ 30% by FLX475 and pembrolizumab combination therapy would be 85% based on the observed data (Table **11.1:2**).
Considering the minimum posterior probability of 80% to achieve ORR ≥ 15% for cohort 1 and ≥ 30% for cohort 2 as well as the overall safety data, the total number of subjects for each cohort will be adjusted after each stage.

- Prior distribution for ORR (P) ~ Unif (0,1)
- Observed data X ~ Binomial (N, P)
- Posterior distribution for ORR, (P| X) ~ Beta (1+X, 1+N-X)







11.2. Populations for Analyses

Treated Set: All subjects who received at least one dose of study drug (FLX475 or pembrolizumab). All demographics, Baseline characteristics, efficacy and safety data will be analyzed using the Treated Set as a primary analysis population.

Tumor Evaluable Set: All subjects who are enrolled, complete at least one cycle of investigational drug, and is evaluable for tumor response based on RECIST, version 1.1. Tumor Evaluable Set will be used for supportive summaries of efficacy data that related to tumor response.

PK Set: All subjects who received at least one dose of FLX475, and have at least one quantifiable plasma concentrations of FLX475.

11.3. Study Endpoints

11.3.1. Primary endpoint

- Objective Response Rate (ORR, complete response + partial response) by RECIST 1.1

11.3.2. Secondary endpoints

- Efficacy in accordance with RECIST 1.1: DCR, TTR, DOR, PFS
- Efficacy in accordance with iRECIST: iORR, iDCR, iTTR, iDOR, iPFS
- Efficacy: OS
- Safety and tolerability: AEs, Laboratory assessments (including hematology, biochemistry, coagulation, urinalysis, vital signs, physical examination, ECG and ECOG)

11.4. Statistical Analysis

The Statistical Analysis Plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any changes from the analyses planned in SAP will be detailed in the Clinical Study Report (CSR).

Final Analysis will be conducted at the time of end of study which was described in the Section **5.2**, and interim analysis will be conducted according to the Section **11.5**.

11.4.1. General considerations

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints unless other specified. As each cohort will enroll target subjects separately and so the analysis will be performed separately for each cohort as well. The data summaries will be presented by stage and overall across stages for each cohort.

Baseline values will be defined as the most recent non-missing measurements collected prior to the first study dose.

11.4.2. Efficacy Analysis

Efficacy analysis will be conducted based on Treated Set and Tumor Evaluable Set. Tumor-related endpoints will be analyzed based on investigator's assessment using RECIST version 1.1, and the result from assessment using iRECIST also be presented.

The primary efficacy endpoint is Objective Response Rate (ORR) defined as the proportion of subjects whose confirmed best overall response is either Complete Response (CR) or Partial Response (PR) according to RECIST version 1.1. The best overall response is the best response recorded from the treatment start date until the earliest of disease progression or last evaluable tumor assessment before events such as start of new anticancer therapy, death, lost to follow-up, etc.

The DCR is defined as the proportion of subjects with confirmed best overall response of CR, PR or SD according to RECIST version 1.1.

The ORR and DCR will be presented with exact 95% Confidence Interval (CI) using the Clopper-Pearson method. Based on the cumulative data about ORR along with prior assumption at each stage, posterior probability of ORR ≥ 15% for cohort 1 and ORR ≥ 30% for cohort 2 would be computed to determine go/no-go decision of the next stage. This cumulative data analysis will be implemented only if at least one response is observed from stage 1 of each cohort.

Time-to-event endpoints, including TTR, DoR, PFS and OS, will be summarized descriptively and graphically using Kaplan-Meier (KM) methodology. Median KM estimates and 95% CI will be presented. For the tumor-related time-to-event endpoints, subjects who have not experience any event (Progressive Disease (PD) or Death) at the time of analysis will be censored at the date of the last evaluable tumor assessment. However, if the subject progresses or dies after two or more consecutive missed assessments or start of new anticancer therapy, the subject will be censored at the time of the last evaluable assessment prior to starting new anti-cancer therapy/missed assessments. If the subject has no evaluable baseline/post-baseline assessment, subject will be censored at the date of first administration of study treatment.

TTR is defined as the time from the date of first administration of study treatment to first documented CR or PR.

DoR is measured from the date of the first observation of tumor response (CR or PR, whichever occurs first) to the date of disease progression or death for the subject with an objected response.

PFS is defined as the time from the date of first administration of study treatment to determination of tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first.

According to iRECIST, Best Overall Response (iBOR) of complete response (CR/iCR), partial response (PR/iPR), stable disease (SD/iSD), Progressive disease (iPD) or unevaluable (iUE) will be derived. iORR, iDCR, iTTR, iDoR and iPFS will be analyzed in the same manner as used analyses in accordance with RECIST 1.1.

iPD is defined as the time point of first iUPD without subsequent iSD, iPR or iCR before study treatment discontinuation.

OS is defined as the duration of time from the treatment start date to time to death from any cause. If subjects survive at the time of analysis, the subject will be censored at the last date of survival confirmed.

11.4.3. Safety Analysis

All adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, graded using NCI-CTCAE version 5.0 and listed by subject.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events (TEAEs). To this end, all adverse events occurring from the first dose of the study treatment through 30 days following cessation of study treatment will be considered 'treatment-emergent'. Adverse events that start before first study treatment and deteriorate under treatment will also be considered as 'treatment-emergent'.

Incidence of TEAEs will be summarized by maximum severity and causal relationship with either FLX475 or pembrolizumab using System Organ Class(SOC) and Preferred Term(PT) of MedDRA. Incidence of ECIs, SAEs, TEAEs leading to dose modification (reduction/interruption), drug discontinuation or death also be summarized respectively, and the list will be provided as appropriately.

Adverse events reported prior to treatment but after informed consent will be provided in a listing.

Laboratory test result will be summarized both quantitatively as well as qualitatively by planned time point. For the quantitative parameter, the actual value and the change from baseline will be summarized using System International (SI) units. Shift table, which display a cross-tabulation of the baseline grade versus the worst grade until ED/EOT will be provided for both of the NCI-CTCAE(v5.0) grade and investigator's clinical significance abnormality assessment.

Vital signs and 12-Lead ECG parameter will be summarized descriptive statistics for the actual value and the change from baseline. In addition, for 12-Lead ECG parameter, the shift table will be presented for the investigator's clinical significance abnormality assessment.

All clinically significant abnormality from the laboratory test, vital signs, and 12-Lead ECG will be classified according to NCI-CTCAE(v5.0) and also be reported as adverse events.

[redacted]

[redacted]

[redacted]

[redacted]

11.5. Interim Analysis

The study is planned initially for 2-stage design for both cohorts but there might be more than 2 stages depending on the results for each cohort. Based on the initial plan with 2-stage design, the interim analysis for each cohort will be performed when the initial 10 subjects of each cohort completes 4 cycles (or 12

weeks; after 2nd response assessment) or withdrawn from the study, whichever occurs first. At this time both efficacy and safety results as well as any available PK and PD data will be reviewed by the IDMC. The number of subjects for the next stage will be determined based on the interim data analysis as well. Study discontinuation due to futility may be recommended by the IDMC to the Sponsor. More details about the decision making based on the interim analysis will be described in charter.

11.6. Data Monitoring Committee (DMC)

The Independent Data Monitoring Committee (IDMC) consisting of investigators (other experts not otherwise involved in the study might be joined in the committee) will be established in this study to ensure external, objective medical and/or statistical review of safety and/or efficacy issues, to protect the ethical and safety interests of subjects, and to protect the scientific validity of the study.

The Safety Review Meeting (SRM) will performed as needed to oversight of study data and monitoring process. The SRM will consist of the sponsor, the study medical monitor and other members deemed appropriate and the investigators. All AEs, SAEs and any other pertinent information collected will be reviewed by SRM.

The tasks and responsibilities of the IDMC and SRM will be specified in charter.

12. DATA COLLECTION AND MANAGEMENT

12.1. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. A quality assurance audit/inspection of this study may be conducted by the sponsor, sponsor's designees, IRB/IEC or regulatory authorities. Audits will be carried out independently apart from routine monitoring and quality control activities.

12.2. Electronic Case Report Forms (eCRFs)

Clinical data will be entered on eCRFs for transmission to the Sponsor via the electronic data capture system. The system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials, and is fully compliant with Code of Federal Regulations (CFR) 21 part 11 and local regulatory requirements. The development, maintenance, and data management of the eCRF is performed by the CRO entrusted by Sponsor according to CRO's standard operating procedures.

Data entry will be performed by the sites, and investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. Data on eCRFs must correspond to and be supported by source documentation maintained at the investigational site. At the monitoring visits, eCRFs will be verified against source documentation. Electronic consistency checks and manual review will also be conducted to identify any errors or inconsistencies in the data.

eCRFs will be considered complete when all missing and/or incorrect data have been resolved, and signed by the investigator to ensure data accuracy, reliability, and completeness. In case Sponsor determine study termination, EDC system can be closed without data cleaning process.

12.3. Source Documentation

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary to substantiate the integrity of the data collection. The Principal Investigator or designee will prepare and maintain adequate and accurate study documents and trial records that include all observations and other pertinent data for each subject.

12.4. Data Protection

The anonymity of participating subject must be maintained. Each subject will be assigned a unique identifier, and any individual records or datasets that are transferred to the sponsor will contain the identifier only; subject's name or any information which would make the subject identifiable will not be transferred. Study subject medical records will be maintained in a confidential manner.

Access to the EDC system is available to authorized users via the study's internet website, where an assigned username and password are required for access. The EDC system is in compliance with applicable data protection guidelines and regulations.

13. ETHICAL CONSIDERATIONS

13.1. Ethical Conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements

13.2. Informed Consent Process

The nature and purpose of the study shall be fully explained to each subject (or their legally responsible guardian).

Written informed consent must be obtained from each subject (or guardian) prior to any study procedures being performed. The investigator will keep the original signed copies of all consent forms in his/her files and will provide a duplicate copy to the subject.

The consent documents to be used for the study shall include all the elements of informed consent in compliance with ICH GCP and be reviewed and approved by the appropriate IEC/IRB prior to use. A copy of the letter indicating IEC or IRB approval must be provided to the Sponsor prior to the study initiations.

13.3. Institutional Review Board or Ethics Committee

This study will be conducted in accordance with the Declaration of Helsinki and its most recent amendments and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations, and in compliance with GCP guidelines.

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with Health authority ICH GCP and local requirements as applicable.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g. advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority as applicable.

13.4. Financing and Insurance

Financial aspects of the study are addressed in a separate clinical trial agreement. The Sponsor will provide insurance cover for the clinical study as required by national regulations.

14. SOURCE DOCUMENTATION, RECORD RETENTION AND MONITORING

14.1. Source Documentations

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring plan (or other equivalent document).

14.2. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 25 years after study completion the last approval of marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

14.3. Study Monitoring

The study will be monitored to ensure that it is conducted and documented according to the protocol, GCP, and all applicable regulatory requirements. On site visits will be made at appropriate times during the period of the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the eCRFs.

The principal investigator will make available to the monitor source documents, medical records, and source data necessary to complete eCRFs. In addition, the principal investigator will work closely with the monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

14.4. Site Inspections / Audit

Representatives of the sponsor's clinical quality assurance department or designee may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and site staffs are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

14.5. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

14.6. Publication Policy

Both the use of data and the publication policy are detailed within the clinical study agreement. The principal investigator should be aware that intellectual property rights (and related matters) generated by the principal investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or their designee will solely own all right and interest in any materials, data and intellectual property rights developed by principal investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, principal investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or their designee, as will be set forth in the clinical study agreement.

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16. APPENDICES

Appendix 1 List of Abbreviations and Definitions of Terms

Abbreviation/ Acronym	Definition
ADL	Activities of daily living
AEs	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC_{0-24}	Area under the plasma concentration time curve from 0 to 24hr
BCG	Bacillus Calmette–Guérin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendment
Cmax	Maximum concentration
CNS	Central Nervous System
CPI	Checkpoint inhibitor
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography

Abbreviation/ Acronym	Definition
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EP	Evaluable Population
FDA	Food and Drug Administration
GC	Gastric cancer
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HNSCC	Head and neck squamous cell carcinoma
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iCPD	immune Confirmed Progressive Disease
iCR	Immune-based complete response
IEC	Independent Ethics Committee
INR	International normalized ratio
iPR	Immune-based partial response

Abbreviation/ Acronym	Definition
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Modified RECIST for immunotherapies
iSD	Immune-based stable disease
ITT	Intent-to-treat data set
iUPD	Immune-based unconfirmed progressive disease
IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactase dehydrogenase
mAb	Monoclonal antibody(ies)
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically-based pharmacokinetics
PD	Progressive disease; pharmacodynamics
PFS	Progression-free survival
PG	Pharmacogenomics
PI	Principal investigator

Abbreviation/ Acronym	Definition
PO	By mouth
PR	Partial response
PK	Pharmacokinetics
PS	Performance status
PT	Preferred term, prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SOPs	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus
t½	Terminal half-life
tbd	To be determined
TEAEs	Treatment-emergent adverse events
TEMAV	Treatment-emergent markedly abnormal laboratory values
tmax	Time to maximum concentration
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TTR	Time to response
UA	Urinalysis
UC	Urothelial carcinoma

Abbreviation/ Acronym	Definition
ULN	Upper limit of normal
US	United States
Vz/F	Oral volume of distribution
WBC	White blood cell
WHO DD	World Health Organization Drug Dictionary
WOCBP	Women Of Childbearing Potential

Appendix 2 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

The Common Terminology Criteria for Adverse Events (CTCAE v5.0, published 27 Nov 2017) provides descriptive terminology to be used for adverse event reporting in the clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE v5.0 have been correlated with MedDRA LLT (Lowest Level Term).

The CTCAE v5.0 grading refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL[b]
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events.

a. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: Cancer Therapy Evaluation Program, NCI. CTCAE v5.0.

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddra.org

Appendix 3 Eastern Cooperative Oncology Group(ECOG) Performance Status Scale

ECOG Performance Status Scale Definitions Rating Criteria	
Score(Grade)	**Status**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Appendix 4 New York Heart Association (NYHA) Cardiac Disease Classification

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for heart failure patients based on cardiac functional capacity. Based on NYHA definitions, subjects are to be classified as follows:

Class	NYHA Status
I	Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of activity; they are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA = New York Heart Association.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-6.

Appendix 5 Description of the iRECIST Process for Assessment of Disease Progression

- ***Assessment at Screening and Prior to RECIST 1.1 Progression***

Until radiographic Progressive Disease (PD) based on RECIST 1.1, there is no distinct iRECIST assessment.

- ***Assessment and Decision at RECIST 1.1 Progression***

For subjects who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to allow a subject to continue to receive study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table **A5:1.**). This decision by the investigator should be based on the subject's overall clinical condition.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir

  Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions -Target.

The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions - Non-target.

- ***Assessment at the Confirmatory Imaging***

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (immune-based stable disease/immune-based partial response/immune-based complete response [iSD/iPR/iCR]).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered Progressive Disease (PD) by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial Progressive Disease (PD) threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

- ***Management Following the Confirmatory Imaging***

If repeat imaging does not confirm Progressive Disease (PD) per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If Progressive Disease (PD) is confirmed, subjects will be discontinued from study treatment.

NOTE: If a subject has immune confirmed progressive disease (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section **9.1.1**

- ***Detection of Progression at Visits After Pseudo-progression Resolves***

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- **Target lesions**
  - Sum of diameters reaches the Progressive Disease (PD) threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- **Non-target lesions**
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- **New lesions**
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated.

Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial Progressive Disease (PD), with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details are provided in the iRECIST publication (Seymour, et al., 2017).

Table A5:1. Imaging and Treatment after First Radiologic Evidence of Progressive Disease in Subjects Receiving FLX475 and Pembrolizumab

- ***Clinical stability is defined as the following:***
  - Absence of symptoms and signs indicating clinically significant progression of disease

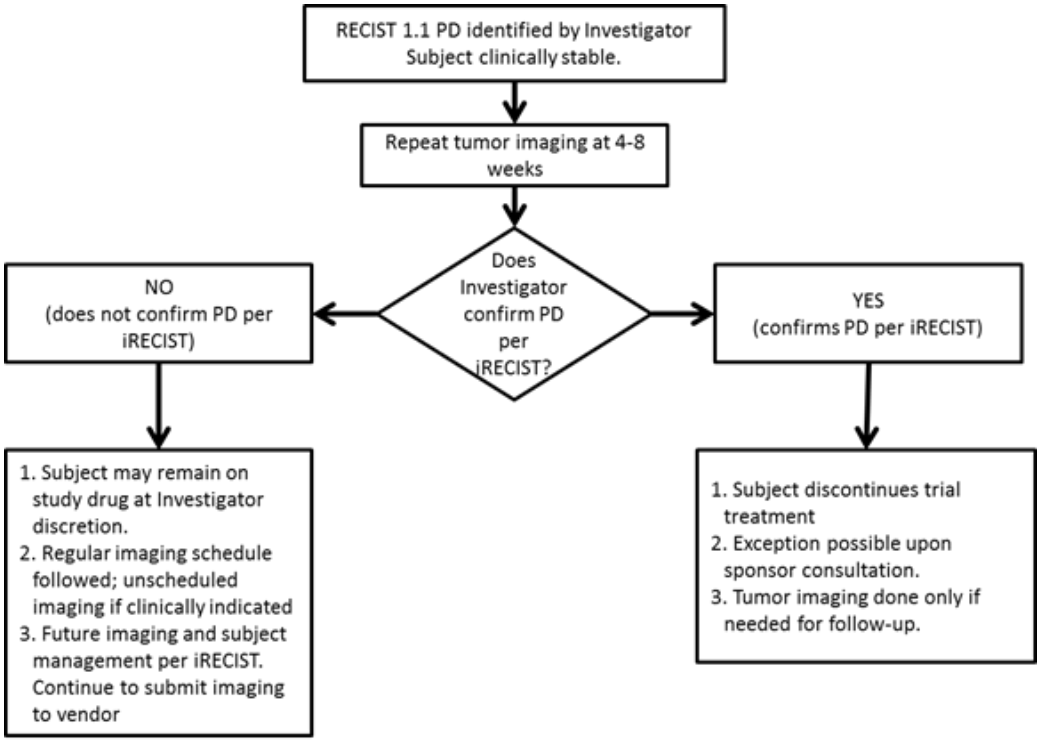
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

Source: Lancet Oncol. 2017 March ; 18(3): e143–e152

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure A5:1 **Imaging and Treatment for Clinically Stable Participants Treated with pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator**



Appendix 6 Prohibited Medications and Therapies

The following is a list of all medications, therapies (including procedures) that are prohibited while the subject is enrolled in this study. Subjects receiving any of these medications at study entry should discontinue the treatment or be switched to a different medication with similar pharmacology prior to starting study treatment. Subjects who receive any of these medications during the Treatment Phase must discontinue study treatment.

Table A6:1. Medications that potentially prolong the QT interval

A list of medications known to cause QTc interval prolongation is provided in the table below and is also available at the following link: https://crediblemeds.org/index.php/drugsearch. This list is not all-inclusive.

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10–25)		4
Amiodarone (cordaron)	58 days (15–142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite T1/2 = 7–10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		
Clarithromycin	Non-linear PK3-4 hr (250mg Q12) 5–7 hr (500 mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopryramide	6.7 hr (4-10)	36	
Dofetilide	10 hours	48	
Dolesetron	8.1 hours		
Domperidone	7-8 hours	48	

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	*Each salt form has different Half-Life*		
Felbamate	20–23 hours		5
Flecainide	20 hours (12–27)		5
Foscarnet	87.5 +/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12–29 hours		6
Gatifloxacin	7–14 hours	48	
Gemiflozacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6–10 days (variable among individual)		45
Haloperidol	18 +/-5 hours		5
Ibutilide	6 hours (2–12) *variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isardipine	8 hours (multiple metabolites)	48	
Levofloxacin	6–8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 days for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hours (10–50)		7
Mesoridazine	24–48 hours (animal study)		10
Methadone	15–30 hours		7
Moexipril/HCTZ	2–9 hour (include active metabolite) for moexipril; 5.6–14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2-hour post IV infusion	12	

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4 +/- 1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3–4 hours for PA and NAPA (active metabolite)	24	
Protriptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3–4 hours in children	36	
Quinine	4–5 hours		
Risperidone	3–20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T1/2 = 21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16–30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5–7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20–40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/- 2 hours for parent comp. 11 +/- 2 hours for OVD (active metabolite)	60	
Ziprasidone	7 hours	36	
Zolmitriptan	2.8–3.7 hours (higher in female)	18	

*Weakly associated with Torsades de pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QT prolonged drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

Source: 1. Physician's Desk Reference 2002; 2. Facts and Comparison (update to June 2005); 3. The Pharmacological Basis of Therapeutics 9th Edition, 1999.

Table A6:2. Known Strong Cytochrome P450 (CYP)3A4 Inhibitors or Inducers

Medication Type	Drug Names
CYP3A4 Inhibitors	
Strong inhibitors	boceprevir, clarithromycin, conivaptan, grapefruit-containing products, indinavir, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, telithromycin
CYP3A4 Inducers	
Strong inducers	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort

17. EXTENSION PART

The extension part will provide continued access to FLX475 combined with pembrolizumab to subjects who have previously participated in HM-CCRI-201 study and are ongoing from the treatment with clinical benefit.

The primary objective of the extension part mainly is to provide continued treatment with FLX475 combined with pembrolizumab without the previous study procedures that intended to collect data for further analysis (e.g. efficacy, safety, biomarker, etc.). Survival and post-therapy long-term follow-up will also be discontinued.

17.1. Study Population

A subject will be eligible for inclusion in the extension part only if all of the following criteria are met:

1. Provision of signed / dated inform consent for the extension part.
2. Currently participating in HM-CCRI-201 study and is receiving treatment with FLX475 in combination with pembrolizumab.
3. Continued ability to swallow tablets without difficulty and retain orally administered study treatment.
4. For female subjects of childbearing potential, must be willing to continue to follow contraceptive guidance during the treatment period and for at least 120 days after the last dose of study treatment (refer to Section 9.2.4.).
5. For male subjects, must agree to continue to use 2 adequate methods of contraception, one of which must be a barrier method, during the study period and 120 days after the final dose of study treatment.

17.2. Study Procedures / Assessments

The Schedule of Procedures / Assessments is presented in the following Flow Chart A.

Study visits will occur on Day 1 (±3 days) of every cycle of 21 days, End of Treatment (EOT) and 30 days (+7 days) after the last dose of study treatment (Safety follow-up visit). Treatment cycles will be counted continuously regardless of dose interruptions (assessments corresponding to each cycle should be performed regardless of study drug administration). Unscheduled visit can be arranged when necessary. When a subject is discontinued from the study treatment, EOT and Safety follow-up visit will be performed, however, survival and post-therapy long-term follow-up will not be performed.

Tumor imaging and disease assessments will be performed throughout the study in accordance with local clinical practice and the appropriate assessment criteria as determined by the investigator to decide continued study participation and treatment with FLX475 combined with pembrolizumab. Only subjects considered by the investigator to be experiencing clinical benefit may continue on study treatment. Subjects will continue to receive study treatment for a maximum of 35 cycles (approximately 2 years).

Safety assessments will be proceeded through routine physical examination, ECOG performance status, vital sign measurement, 12-Lead electrocardiograms, echocardiograms or multiple-gated acquisition scans (when clinically required), laboratory assessments, and monitoring of adverse events (including serious adverse events).

Flow Chart A: Schedule of Procedures/Assessments for the Extension Part

Study Period/Cycle	Treatment (Each cycle = 21 days)		End of Treatment (EOT) Visit [b]	Safety Follow-up [c]
	Scheduled Visit (Day 1 of every cycle)	Unscheduled Visit [a]		
Cycle day	1 (±3)	NA		30 (+7) days after the last dose
General Procedure				
Informed Consent [d]	X			
Concomitant Medication	X	(X)	X	X
Investigational Product Dispensing and Administration				
FLX475 In-clinic Administration [e]	X			
Pembrolizumab Administration [e]	X			
FLX475 Dispensing [f]	X			
Clinical Procedure/ Assessments				
Physical Examination [g]	X	(X)	X	
ECOG Performance status	X	(X)	X	
Vital Signs [h]	X	(X)	X	
Triplicate 12-Lead ECGs [i]	X	(X)	X	X [s]
ECHO or MUGA [j]				
AE/SAE Assessment [k]	X	(X)	X	X
Diary Card Dispensed/Collected	X		X	
Drug Accountability	X		X	
Laboratory Assessments				
Serum Chemistry [l]	X	(X)	X	
Hematology [m]	X	(X)	X	
Coagulation Tests [n]	X	(X)	X	
Thyroid Function Tests [o]	X	(X)	X	
Urinalysis [p]	X	(X)	X	
Pregnancy Test [q]	X	(X)	X	
Disease Assessments				
Tumor Imaging/Staging (CT/MRI Scan) [r]	Radiological and clinical response assessments will be performed per investigator's discretion until Progressive Disease (PD) is confirmed			
Response Assessment [r]				

Pre-dose assessment (e.g. ECGs) should be obtained at study visits even when study treatment is being held or not given. All time points of the assessments are based on FLX475 administration.

a. Unscheduled visits can be arranged if necessary. Study procedures will be at the discretion of the investigator.
b. All Early Discontinuation / End of Study Treatment (ED/EOT) assessments must be performed within 14 days following the subject's last administration of study treatment and prior to initiation of any other treatment, whichever comes first.
c. Safety follow-up visit will be scheduled 30 days (+7 days) from the final dose of study treatment. Follow up contact via telephone with the subject could be allowed unless any assessment must be performed for resolution of treatment-related AE.
d. Informed consent must be obtained before the subject undergoes any study-specific procedures (only at initial visit to continue on in the extension part).
e. On days when a clinical visit, the dose of FLX475 will be administered in the clinic after the specified visit assessments and procedures are performed. In addition, the dose of FLX475 should be self-administered in the clinic on Day 1 of each cycle. After a new supply of drug has been dispensed for that cycle, a diary card will be provided to each subject for recording of all dose administration information for drug accountability purposes. Pembrolizumab will be administered at a dose of 200mg IV over 30 minutes on Day 1 of each cycle. Pembrolizumab infusion should occur at least 1 hour after the dose of FLX475 is administered in the clinic. (Treatment cycles will be counted continuously regardless of dose interruptions and assessments corresponding to each cycle should be performed regardless of study drug administration).
f. Dispensing of 3-week supply of FLX475 to the subject with instruction for self-administration at home.
g. Weight measurement should be performed on Day 1 of each cycle and at ED/EOT.
h. Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected with the subject in a sitting position. Vital signs will be assessed pre-dose at Day 1 of each cycles and at ED/EOT.
i. Triplicate ECGs with tracings approximately 2 minutes apart must be collected in digital format on designated calibrated ECG equipment after at least 10 minutes of quiet rest in supine position. Meals should not be served shortly before ECGs. Pre-dose ECGs assessment will be performed on Day 1 of each cycles, at ED/EOT and at Safety follow-up visit (30 days (+7 days) from the final dose of study treatment).
j. Assessment may be performed if clinically required at investigator's discretion.
k. All AEs must be recorded and followed through 30 days following cessation of study treatment (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first. All SAEs must be reported after the consent form is signed through 90 days following cessation of study treatment, or 30 days after final dose if the subject initiates new anticancer therapy, whichever occurs first.

l. Serum Chemistry: includes sodium, potassium, chloride, total protein, bicarbonate, albumin, calcium, magnesium, phosphorous, glucose, BUN, creatinine (or CrCl), uric acid, total bilirubin, ALP, LDH, AST, ALT, amylase and lipase. Pre-dose serum chemistry to be obtained at Day 1 of each cycles and at ED/EOT.

m. Hematology: WBC, RBC, ANC, hemoglobin, hematocrit, MCV, MCH, platelets, and WBC differential. Blood sampling for hematology to be obtained pre-dose at Day 1 of each cycles and at ED/EOT.

n. Coagulation Tests (PT, PTT or aPTT, and INR) should be performed pre-dose on day 1 of every cycle and at ED/EOT.

o. Thyroid function tests should be performed pre-dose on Day 1 of every odd-numbered cycle during study treatment (e.g., Cycle 3, 5, etc.) and at ED/EOT. Thyroid panel should include (1) Triiodothyronine (T3) or Free Triiodothyronine (FT3), (2) Free Thyroxine (FT4), and (3) Thyroid Stimulating Hormone (TSH).

p. Urinalysis will include specific gravity, pH, blood, protein, glucose, ketones and bilirubin (microscopic UA with WBC, RBC, epithelial cells, bacteria, casts and crystals, only if necessary).

q. Pregnancy testing (urine or serum) will be performed on Day 1 of every odd-numbered cycles (e.g., Cycle 3, 5, etc.) and at ED/EOT.

r. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Radiological and clinical response assessments will be performed at any time per investigator's discretion until objective disease progression is confirmed.

s. Triplicate ECGs on Safety follow-up visit is to be performed only on subjects who have experienced QTc interval prolongation during the study.

17.3. Study Visit

Scheduled Visit

Scheduled visits will occur on Day 1 (±3 days) of every cycle (1 cycle = 21 days).

- Obtain informed consent before the subject undergoes any study-specific procedures / assessments (only at initial visit to continue on in the extension part).
- Assess concomitant medication.
- Perform physical examination (weight measurement).
- Obtain vital signs.
- Assess ECOG performance status.
- Perform pre-dose 12-Lead triplicate ECGs on Day 1 of each cycles.
- Assess AEs/SAEs, severity and possible relationship with study drugs.
- Perform clinical laboratory assessments (including chemistry, hematology, coagulation, urinalysis, thyroid function test, pregnancy test).
- Dispense study drug.
- Assess study drug compliance.
- Perform radiological and clinical response assessments per investigator's discretion when Progressive Disease (PD) is suspected.

Unscheduled Visit

Unscheduled visit can be arranged when necessary. Study procedures / assessments will be at the discretion of the investigator and may include,

- Assess concomitant medication.
- Perform physical examination (weight measurement).
- Obtain vital signs.
- Assess ECOG performance status.
- Perform 12-Lead triplicate ECGs.
- Assess AEs/SAEs, severity and possible relationship with study drugs.
- Perform clinical laboratory assessments (including chemistry, hematology, coagulation, urinalysis, thyroid function test, pregnancy test).
- Perform a urine or serum pregnancy test for women of child bearing potential if clinically indicated.
- Perform radiological and clinical response assessments per investigator's discretion when Progressive Disease (PD) is suspected.

End of Treatment (EOT) Visit

All subjects will undergo procedures / assessments for the EOT visit within 14 days following the last administration of study treatment and prior to initiation of any other treatment, whichever comes first.

- Assess concomitant medication.
- Perform physical examination (weight measurement).
- Obtain vital signs.
- Assess ECOG performance status.

- Perform 12-Lead triplicate ECGs.
- Assess AEs/SAEs, severity and possible relationship with study drugs.
- Perform clinical laboratory assessments (including chemistry, hematology, coagulation, urinalysis, thyroid function test, pregnancy test).
- Perform a urine or serum pregnancy test for women of child bearing potential if clinically indicated.
- Assess study drug compliance.

30-Day Safety Follow-Up Visit (+7 days)

Unless subjects withdraw consent or are lost to follow-up, subjects who discontinue study treatment will be followed for acquisition of safety information for 30 days (+7 days) after the final dose of study treatment. All AEs that occur prior to the Safety follow-up visit should be recorded. AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Subject who followed the Safety follow-up period should undergo assessment of concomitant medication, 12-Lead triplicate ECGs (3 separate ECGs approximately 2 minutes apart; 10 minutes resting prior to first ECG; only on subjects who have experienced QTc interval prolongation during the study), AEs/SAEs assessment 30 days (+7 days) after the final dose of study treatment.

Note: Follow-up contact via telephone with the subject could be allowed unless any assessment must be performed for resolution of treatment-related AE.

End of Study

The end of study is defined as the date when the last subject, last visit (LSLV) occurs or the date at which all required Safety follow-up data and documentation have been received by Sponsor, whichever occurs later.

17.4. Study Treatment

Study Treatment	Formulation	Dose*	Route of Administration	Sourcing
FLX475	Tablets	100 mg, QD	Oral	Provided centrally by the Sponsor
Pembrolizumab	Solution for infusion	200 mg, Q3W	IV infusion	Provided centrally by the Sponsor

IV = intravenous, Q3W = once every 3 weeks, QD = once daily
* Current ongoing dose entering into extension part may vary between subjects (e.g. due to dose modification)

Subjects will receive FLX475 orally once daily (QD) in conjunction with pembrolizumab by IV once every 3 weeks (Q3W) until subject withdrawal from the study, confirmed progression of cancer, intolerable study treatment-related toxicity despite appropriate dose modification and supportive treatment, the development of intercurrent illness that precludes continued study treatment, pregnancy or breastfeeding, substantial noncompliance with study procedures, loss to follow-up, or study termination by the Sponsor, whichever occurs first. Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

FLX475 tablets are to be taken with water orally once a day approximately at the same time each day in every 3-week cycle (21 days). Fasting is not required for FLX475 administration. On clinic visit days, the dose of FLX475 will be administered in the clinic after the specified assessments and procedures are

performed. FLX475 should be taken approximately 1 hour before the pembrolizumab infusion, on days when pembrolizumab is also administered (i.e., Day 1 of each cycle).

Pembrolizumab 200 mg will be administered as an IV infusion over 30 minutes on Day 1 of every 3-week treatment cycle (i.e., every 21 days [±3 days]) after all procedures and assessments have been completed, and approximately 1 hour after the Day 1 dose of FLX475. The site staff should make every effort to ensure that the infusion duration be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time of 25 to 40 minutes). The Pharmacy Manual contains specific instructions for the preparation and administration of the pembrolizumab infusion.

Discontinuation of study treatment does not represent withdrawal from the study. The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

FLX475 treatment must be discontinued but the subject should continue to be monitored in the study for any of the following reasons:

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.3.1.

Pembrolizumab treatment must be discontinued but the subject should continue to be monitored in the study for any of the following reasons:

- Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 7.3.2.

Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving [2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of FLX475] beyond the date when the initial CR was declared.

The reason for discontinuation of FLX475, pembrolizumab, or both will be documented. If a subject discontinues study treatment, the subject will enter the Safety follow-Up phase and complete protocol-specified End of Treatment and Safety follow-up visits, procedures unless the subject withdraws consent. The investigator should confirm whether a subject will discontinue study treatment but agree to continue protocol-specified, post-treatment study visits, procedures, or whether the subject withdraws consent or is lost to follow-up. If a subject withdraws consent, the date will be documented in the source documents. Subjects may withdraw their consent for study participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the study. Furthermore, it may mean that further subject follow-up on safety cannot occur. If subject want to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for study participation and explain the options for continued safety follow up after withdrawal. The investigator will complete the appropriate eCRF, indicating the primary reason for discontinuation. In addition, the date of final dose of study treatment(s) will be recorded on the appropriate eCRF.

Following sections will also be applied to the extension part:

7.3. Dose Modification

7.5. Identify of Investigational Products

7.6. Prior and Concomitant Therapy

17.5. Study Assessment

17.5.1. Efficacy Assessment (Tumor Imaging and Disease Assessment)

RECIST 1.1 will be used as the primary measure for assessment of tumor response and progression, date of Progressive Disease (PD), and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment).

CT scans are preferred over other tumor imaging methods. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same type of scan should be used consistently for each subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Note: for the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site or the radiological reviewer located at the site or at an offsite facility.

- In general, imaging should include the chest (CT), and abdomen and pelvis (CT or MRI).
- Imaging should include other known or suspected sites of disease.
- If brain scans are performed, magnetic resonance scans are preferred. However, CT scans are acceptable, if MRI is medically contraindicated. The brain scan (MRI pre- and postgadolinium or CT with contrast) will be performed as clinically indicated, and within a target of 1 week but no more than 2 weeks following achievement of a CR. For subjects with a history of protocol-eligible, treated brain metastases, a brain scan will be required.

17.5.1.1. Timing of Tumor Imaging

There will no longer be periodical tumor imaging and disease assessment required in the extension part of the study.

Tumor imaging and disease assessment will only be performed throughout the study in accordance with local clinical practice and the appropriate assessment criteria as determined by the investigator to decide continued study participation and treatment with FLX475 combined with pembrolizumab. Tumor imaging and disease assessment will be performed per investigator's discretion until Progressive Disease (PD) is confirmed.

17.5.2. Safety Assessment

Safety assessments will be proceeded through routine physical examination, vital sign measurement, 12-Lead electrocardiograms, echocardiograms or multiple-gated acquisition scans (when clinically required), laboratory assessments, and monitoring of adverse events / serious adverse events using CTCAE v5.0 (Appendix 2).

Following sections will also be applied to the extension part:

9.2.1. Adverse Events and Events of Clinical Interest (AEs and ECIs)
9.2.2. Serious Adverse Events, Events of Clinical Interest, and Events Associated with Special Situations
9.2.3. Overdose
9.2.4. Pregnancy, Contraception, and Breastfeeding

AEs, ECIs, SAEs and Events Associated with Special Situations

All AEs or events of clinical interest (ECIs) that occur after the consent form is signed through 30 days following cessation of study treatment must be reported on the eCRF by the investigator. All AEs must be recorded and followed through 30 days following cessation of study treatment (or 30 days after final dose if the subject initiates new anticancer therapy), or until resolution, whichever comes first.

All SAEs defined in Section 9.2.2. must be reported after the consent form is signed through 90 days following cessation of study treatment, or 30 days after final dose if the subject initiates new anticancer therapy, whichever occurs first.

Refer to Section 9.2.2. for more information on SAEs, ECIs and Events Associated with Special Situations.

Laboratory Assessments

Laboratory assessments will be performed at the times indicated in Flow Chart A. Subjects should be in a seated or supine position during blood collection. All assessments will be performed at a local laboratory at the investigating site.

Refer to Table 9.2.1 for categories required for laboratory assessments.

Vital Signs and Weight Measurements

Blood pressure, pulse rate, respiratory rate and body temperature will be taken with the subject in a sitting position.

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Flow Chart A by a validated method.

Refer to Section 9.2.6. for further information on vital sign measurement.

Electrocardiograms

ECGs will be recorded and evaluated at the clinical study (local) site for the purposes of real-time cardiac safety monitoring.

The 12-Lead ECG will be performed in triplicate in supine position (3 separate ECGs approximately 2 minutes apart; 10 minutes resting prior to first ECG). ECGs will precede blood sample if they are to be overlapped.

Triplicate 12-lead ECGs will be performed at the time points specified in Flow Chart A (note that designated “Pre-dose” ECGs should be obtained at study visits even when study treatment is being held / not given).

Refer to Section 9.2.8. for further information on electrocardiogram.

Following section will also be applied to the extension part:

9.2.7. Physical Examinations / ECOG PS

17.6. Safety Monitoring and Reporting

Following sections will also be applied to the extension part:

10.1.1. Reporting of Serious Adverse Events
10.1.2. Reporting of Pregnancy and Breastfeeding
10.1.3. Reporting of Events Associated with Special Situations
10.1.4. Expedited Reporting
10.1.5. Regulatory Reporting of Adverse Events

17.7. Statistical Consideration and Evaluation

As the main purpose of the extension part is to provide continued treatment with FLX475 combined with pembrolizumab without the previous study procedures that intended to collect data for further analysis, only the limited analysis for the safety data will be performed [redacted]

17.8. Data Collection and Management

Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. A quality assurance audit/inspection of this study may be conducted by the sponsor, sponsor's designees, IRB/IEC or regulatory authorities. Audits will be carried out independently apart from routine monitoring and quality control activities.

Following sections will also be applied to the extension part:

12.2. Electronic Case Report Forms (eCRFs)
12.3. Source Documentation
12.4. Data Protection

17.9. Ethical Consideration

Ethical Conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements.

Following sections will also be applied to the extension part:

13.2. Informed Consent Process
13.3. Institutional Review Board or Ethics Committee
13.4. Financing and Insurance

17.10. Source Documentation, Record Retention and Monitoring

Following sections will also be applied to the extension part:

14.1. Source Documentations
14.2. Record Retention
14.3. Study Monitoring
14.4. Site Inspections / Audit
14.5. Protocol Amendments
14.6. Publication Policy